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THE WESTERN Journal of Medicine

VOLUME 131 • NUMBER 1 JULY 1979

1 *Chemotherapy of Disseminated Testicular Cancer*
LAWRENCE H. EINHORN, MD, and STEPHEN D. WILLIAMS, MD

4 *Fiberoptic Bronchoscopy in Diagnosis of Opportunistic Lung Infections—Assessment of Sputa, Washings, Brushings and Biopsy Specimens*
SAWTANTRA K. CHOPRA, MD, and ZAB MOHSENIFAR, MD

MEDICAL PROGRESS
8 *High Altitude Medical Problems* HERBERT N. HULTGREN, MD

SPECIALTY CONFERENCE
24 *Pulmonary Arteriovenous Communications in the Lung*
Moderator: EUGENE D. ROBIN, MD; Participants: JOSEPH CUMMISKEY, MD; EUGENE D. ROBIN, MD; JAMES THEODORE, MD; GEORGE CAUGHEY, BS; MICHAEL GORIS, MD; S. J. SALFEN, MD; ALLAN HANCE, MD; ANTONIUS VAN KESSEL, BS; PATRICIA LYNNE-DAVIES, MD, and MICHAEL PINSKY, MD
Pulmonary Rounds, Stanford University School of Medicine

MEDICAL STAFF CONFERENCE
36 *Drug-Induced Liver Disease* Chief Discussant: ROBERT K. OCKNER, MD

IMPORTANT ADVANCES IN CLINICAL MEDICINE
46 *Chest Diseases—Epitomes of Progress*

EDITORIALS
52 • *Some Conceptual and Practical Problems Facing Medicine* • *Mount Olympus Revisited* • *Lessons From Skull Films* • *Implications of Successful Combination Chemotherapy for Testicular Germ Cell Neoplasms*

CASE REPORTS
57 *Ibuprofen-Associated Aseptic Meningitis in Systemic Lupus Erythematosus*
CECIL O. SAMUELSON, JR., MD, and H. JAMES WILLIAMS, MD

59 *Clonidine Hydrochloride Withdrawal Complicating Bilateral Nephrectomy*
LT TIMOTHY P. MATE, MC, USNR; LCDR ARON H. R. SWERDLIN, MC, USNR; RICHARD A. STONE, MD, and CDR STEVEN M. STEINBERG, MC, USN

62 *Thrombocytopenia Associated With Intravenous Heroin Abuse*
RAYMOND TAETLE, MD, and SCOTT BROWNING, MD

CORRESPONDENCE
65 • *Canadian Cooperative Trial on Platelet-Inhibiting Drugs; With Reply by Author* • *VD in China* • *Thoughts After Three Mile Island* • *Patient Care Audits* • *Preventing Dental Caries in Children* • *Of Politics, Smoke Screens and Industry*

ENVIRONMENTAL HEALTH
70 *Health Implications of Increased Coal Use in the Western States* TEE L. GUIDOTTI, MD

MEDICAL EDUCATION
77 *Continuing Education: A Medical School Responsibility?* SIMON A. SAYRE, MD

INFORMATION
82 *Skull Radiography and Professional Liability* LEON A. PHILLIPS, MD

83 *Southern Medical Association Meeting in Las Vegas*

84 *In Memoriam*

Books Received, See Advertising Page 12

★ CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII; OREGON; WASHINGTON; ALASKA, MONTANA AND IDAHO
(See Advertising Page 29)

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THE EMOTIONAL-NEURAL LINK IN DUODENAL ULCER*

How excessive anxiety may induce vagal stimulation of acid-pepsin secretion

A manifestation of emotional stress, excessive anxiety may induce gastric hypersecretion by its effect on central and peripheral neural activity. Hypothalamic mediation of *vagal* activity increases acid and pepsin output,[1,2] leading to exacerbation of the distressing symptoms of duodenal ulcer.

Artist's impression of peripheral nerve ramifying on the surface of gastric mucosal cells. Illustration based on a cross section of gastric wall as seen by scanning electron microscope.

1. Sun DCH: Etiology and pathology of peptic ulcer, chap. 27, vol. 1, in *Gastroenterology*, ed. 3, edited by Bockus HL, *et al*. Philadelphia, W.B. Saunders Company, 1974, pp. 586, 592-593. 2. Palmer ED: *Clinical Gastroenterology*, ed. 2. New York. Hoeber Medical Division, Harper & Row, Publishers, 1963, p. 202.

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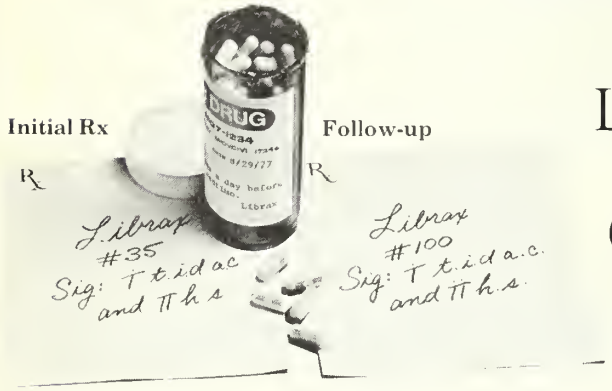

The initial prescription allows evaluation of patient response to therapy.

Follow-up therapy with a prescription for a 2- to 3-week supply of medication usually helps maintain patient gains.

Please consult complete prescribing information, a summary of which follows:

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

How Supplied: Available in green capsules, each containing 5 mg chlordiazepoxide HCl (Librium®) and 2.5 mg clidinium Br (Quarzan®)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50, singly and in trays of 10.

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Tablets
100 tablets
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cimetidine/2 ml.
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cimetidine
hydrochloride
2 ml.
phenol, 10 mg.
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Tagamet®
brand of
cimetidine
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in single-dose vials
and in 8 ml. multiple-dose vials,
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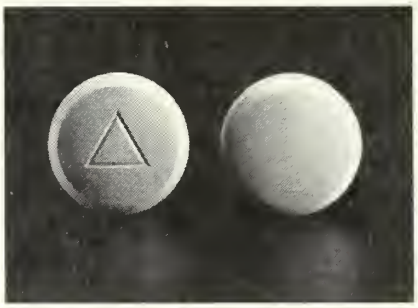
The Maker

Examining a Few Myths About Prescribing.



Increasing pressure is being put on the practicing physician to prescribe drugs generically. You are told that brand–name products are universally "expensive" and generic versions are relatively "cheap." To make this case, the most extreme (rather than typical) price differentials are cited. Thus, consumers are led to believe that such differentials are commonplace. Even your knowledge and your motives as a physician are questioned.

Understandably, these views have created myths. We think it's time to examine them in the light of all the facts and ramifications.

MYTH: There are no differences in quality and performance between brand-name products and their generic counterparts. The corollary is that there are no differences among products made by high-technology, quality-conscious, research-based companies and those made by commodity-type suppliers.

FACT: The Food and Drug Administration does a good job in monitoring a generally excellent drug supply. Still, it has nowhere near the resources to guarantee the quality and bioavailability of all marketed products at any given time. Just a few months ago, for example, it noted that batches of tetracycline HCl capsules which met official monograph requirements were not bioequivalent to a reference product. As you know, there is substantial literature on this subject affecting many drugs, including such antibiotics as tetracycline and erythromycin. The record on drug recalls and court actions affirms strongly that there are differences among pharmaceutical companies and their products. Research-intensive companies have far better records than those that do no research and may practice minimum quality assurance.

MYTH: Industry favors only "expensive" brand names and denigrates all generics.

FACT: PMA companies make 90 to 95 percent of the drug supply, including, therefore, most of the generics. Drug nomenclature is not the important point; it's the competence of the manufacturer and the integrity of the product that count.

Matters.

MYTH: Generic options almost always exist.

FACT: About 55 percent of prescription drug expenditure is for single-source drugs. This means, of course, that for only 45 percent of such expenditure, is a generic prescribing option available.

MYTH: Generic prescriptions are filled with inexpensive generics, thus saving consumers large sums of money.

FACT: Market data show that you invariably prescribe—and pharmacists dispense—both brand and generically labeled products from known and trusted sources, in the best interest of patients. In most cases the patient receives a proven brand product. Savings from voluntary or mandated generic prescribing are grossly exaggerated.

MYTH: Drugs account for a major portion of the rise in health care costs.

FACT: Drugs represent a very small part of such costs. The amount of the health care dollar spent for prescription drugs was about 12 cents in 1967; today it is about 8 cents. And you as a physician are most conscious of how drug therapy can cut hospitalization, avert surgery, reduce office visits and keep patients on the job.

MYTH: Government intrusions into the marketplace will save tax money.

FACT: Government schemes always cost the taxpayer something, and the costs often exceed the benefits. Certainly, any federal "help," such as lists of wholesale drug prices sent to all physicians and pharmacists, will be no exception. Just think of the expense of keeping them current! Moreover, wholesale prices are poor guides to actual transaction prices and even worse guides to retail prices.

The PMA Position

We believe your freedom to prescribe, either by generic or brand name, should be totally unabridged. Otherwise, your prescribing prerogatives and your relationships with patients will be seriously impaired.

The maker does matter

After the myths about price and equivalency have been shattered, one fact stands out more clearly than ever: *The maker does matter.* As always, your best guide to drug therapy for your patients is to select products—both brands and generics—from manufacturers with credentials and performance records you have come to respect.

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J-6999-4

April 1979

Tablets

PERCOCET®-5 (II)

Brief Summary of Prescribing Information

DESCRIPTION Each tablet of PERCOCET®-5 contains 5 mg oxycodone hydrochloride (WARNING: May be habit forming), 325 mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS. 6085 BS

DEA Order Form Required.

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Tablets

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Each tablet contains 5 mg oxycodone HCl (WARNING: May be habit forming) and 325 mg acetaminophen (APAP)

...FOR THOSE WHO CAN'T TOLERATE ASPIRIN

- □ indicated for moderate to moderately severe pain
- □ contains well-tolerated acetaminophen
- □ provides the effective analgesia of oxycodone
- □ scored tablet permits finer titration
- □ convenient, economical q6h dosage

Please see opposite page for brief summary of prescribing information.

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

CRY BABEL—The Nightmare of Aphasia and a Courageous Woman's Struggle to Rebuild Her Life—April Oursler Armstrong. Doubleday & Company, Inc., Garden City, NY, 1979. 252 pages, $8.95.

DIAGNOSTIC METHODS IN VIRAL HEPATITIS—Volume 2 in the series: LABORATORY AND RESEARCH METHODS IN BIOLOGY AND MEDICINE—Editors: P. S. Gardner, Royal Victoria Infirmary, Newcastle-upon-Tyne, England; and Colin R. Howard, London School of Hygiene and Tropical Medicine. Alan R. Liss, Inc., 150 Fifth Ave., New York City (10011), 1978. 92 pages, $12.00 (available in Europe and the Middle East exclusively from European Book Service, Flevolaan 36-38, P.O.B. 124, 1380 AC Weesp, Holland, for 36.00 Dutch Guilders).

ECONOMIC FOUNDATIONS OF NATIONAL HEALTH POLICY—Allan S. Detsky, MD, PhD, The Harvard-M.I.T. Division of Health Sciences and Technology, Boston. Ballinger Publishing Co., 17 Dunster St., Harvard Square, Cambridge, MA (02138), 1978. 265 pages, $20.00.

HOW TO GET ALONG WITH YOUR STOMACH—Nancy Nugent. Doubleday & Company, Inc., 245 Park Ave., New York City (10017), 1979. 276 pages, $3.95 (Paperback).

INTERPRETING THE ELECTROCARDIOGRAM—James S. Fleming, MD, FRCP, Consultant Cardiologist, Northern General, Hallamshire, and Children's Hospital, Sheffield, UK. Update Books Ltd, London, 1979. Available outside the United Kingdom from Update Publishing International Inc., 2337 Lemoine Ave., Fort Lee, NJ 07024. 135 pages, $16.50.

LABORATORY METHODS IN ANTIMICROBIAL CHEMOTHERAPY—Edited by David S. Reeves, MB, BS, MCRPath, Consultant Medical Microbiologist, Southmead Hospital, Bristol; Honorary Consultant, Public Health Laboratory Service, Honorary Clinical Teacher, University of Bristol; Ian Phillips, MA, MD, BChir, MRCP, MRCPath, Professor of Medical Microbiology, University of London, St. Thomas's Hospital Medical School; Honorary Consultant Microbiologist, St. Thomas's Hospital, London; J. David Williams, BSc, MD, MRCPath, DCP, Professor of Medical Microbiology, London Hospital Medical College, Consultant Microbiologist, The London Hospital and the Institute of Urology, Civilian Consultant to the Royal Navy; and Richard Wise, MB, ChB, MRCPath, Consultant Medical Microbiologist, Dufley Road Hospital, Birmingham, Senior Clinical Lecturer, University of Birmingham. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1978. 272 pages, $35.00.

MEDICAL MICROBIOLOGY—13th Edition—Volume 1: MICROBIAL INFECTIONS—J. P. Duguid, BSc, MD, FRCPath, Professor of Bacteriology, University of Dundee; B. P. Marmion, DSc, MD, FRCPath (UK and Aust), FRCP(Ed), Director, Division of Virology, Institute for Medical and Veterinary Science, Adelaide, South Australia; Formerly Professor of Bacteriology, University of Edinburgh; and R. H. A. Swain, MA, MD, FRCP(Ed), FRCPath, FRSE, Formerly Reader in Virology, University of Edinburgh; Formerly Consultant in Virology, The Royal Infirmary, Edinburgh. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 666 pages, $35.00.

MELLONI'S ILLUSTRATED MEDICAL DICTIONARY—Ida Dox, Technical Lexicographer, Medical Communicator, Georgetown University Schools of Medicine and Dentistry; Biagio John Melloni, Professorial Lecturer in Anatomy; Chairman, Department of Medical-Dental Communication, Georgetown University Schools of Medicine and Dentistry; Medical Art Editor, **American Family Physician;** and Gilbert M. Eisner, MD, FACP, Adjunct Associate Professor of Physiology and Biophysics, Georgetown University School of Medicine; Senior Attending Physician, Washington Hospital Center. Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1979. 530 pages, $16.50.

(Continued on Page 14)

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THE NEW AMERICAN MEDICINE SHOW—Discovering the Healing Connection—Dr. Irving Oyle. Unity Press, 113 New Street, Santa Cruz, CA (95060), 1979. 170 pages, $5.95 (Paperback).

NORTHINDRONE—The First Three Decades—Edited by Mary Jean Pramik, Medical Services Department, Syntex Laboratories, Inc., Palo Alto, CA. Syntex Laboratories, Inc., Palo Alto, 1978. 112 pages, available to health care professionals at no charge from Medical Services Dept., Syntex Laboratories, Inc., 3401 Hillview Ave., Palo Alto, CA 94304.

THE POLITICS OF HEALTH CARE—J. H. U. Brown, PhD, Southwest Research Consortium, San Antonio. Ballinger Publishing Company, 17 Dunster Street, Harvard Square, Cambridge, MA (02138), 1978. 151 pages, $15.00.

PRINCIPLES OF CLINICAL ELECTROCARDIOGRAPHY—Tenth Edition—Mervin J. Goldman, MD, Clinical Professor of Medicine, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1979. 415 pages, $12.00.

PSYCHIATRY FOR THE PRIMARY CARE PHYSICIAN—Edited by Arthur M. Freeman III, MD, Professor of Psychiatry, University of Alabama School of Medicine, Director, Psychiatric Consultation-Liaison Service, University of Alabama Medical Center, Chief, Psychiatry Service, VA Medical Center, Birmingtam; Robert L. Sack, MD, Associate Professor of Psychiatry, Director, Psychiatric Consultation-Liaison Service, University of Oregon Health Sciences Center, Portland; and Philip A. Berger, MD, Assistant Professor, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Director, Stanford Psychiatric Clinical Research Center, VA Medical Center, Palo Alto, CA. The Williams & Wilkins Co., 428 E. Preston St., Baltimore (21202), 1979. 422 pages, $19.95.

ROUND-TABLE DISCUSSION ON GENTAMICIN AND TOBRAMYCIN—Royal Society of Medicine International Congress and Symposium Series Number 4—Edited by Robert G. Richardson. Grune & Stratton, Inc., Medical and Scientific Publishers, 111 Fifth Avenue, New York City (10003), 1978. 64 pages, $10.25.

TEXTBOOK OF GERIATRIC MEDICINE AND GERONTOLOGY—Second Edition—Edited by J. C. Brocklehurst, MD, MSc, FRCP(Glas and Ed), Professor of Geriatric Medicine, University of Manchester. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St. (New York City), 10036. 838 pages, $65.00.

TOWARDS EARLIER DIAGNOSIS IN PRIMARY CARE—Fourth Edition—Keith Hodgkin, BM, BCH, FRCGP, FRCP, Previously General Practitioner, Redcar, Yorkshire, and Sir Harry Jephcott Visiting Professor in General Practice, Professor and Chairman of General Practice, Memorial University, Newfoundland, Canada. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 623 pages, $19.50 (softbound).

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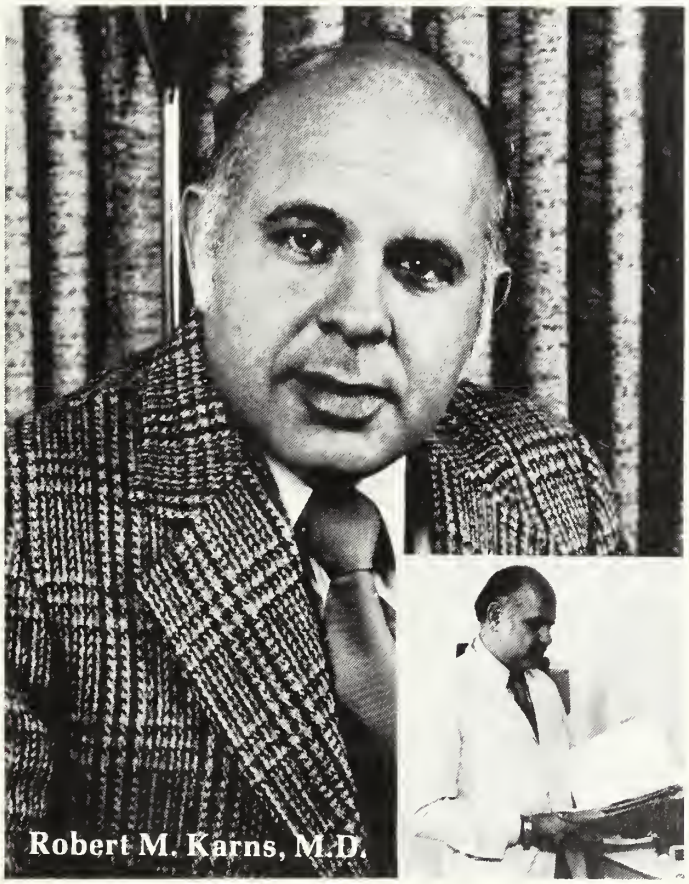

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PRECAUTIONS: Evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

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A syndrome resembling lupus erythematosus has been reported with oral maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

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A syndrome resembling lupus erythematosus has been reported in patients on oral maintenance therapy (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

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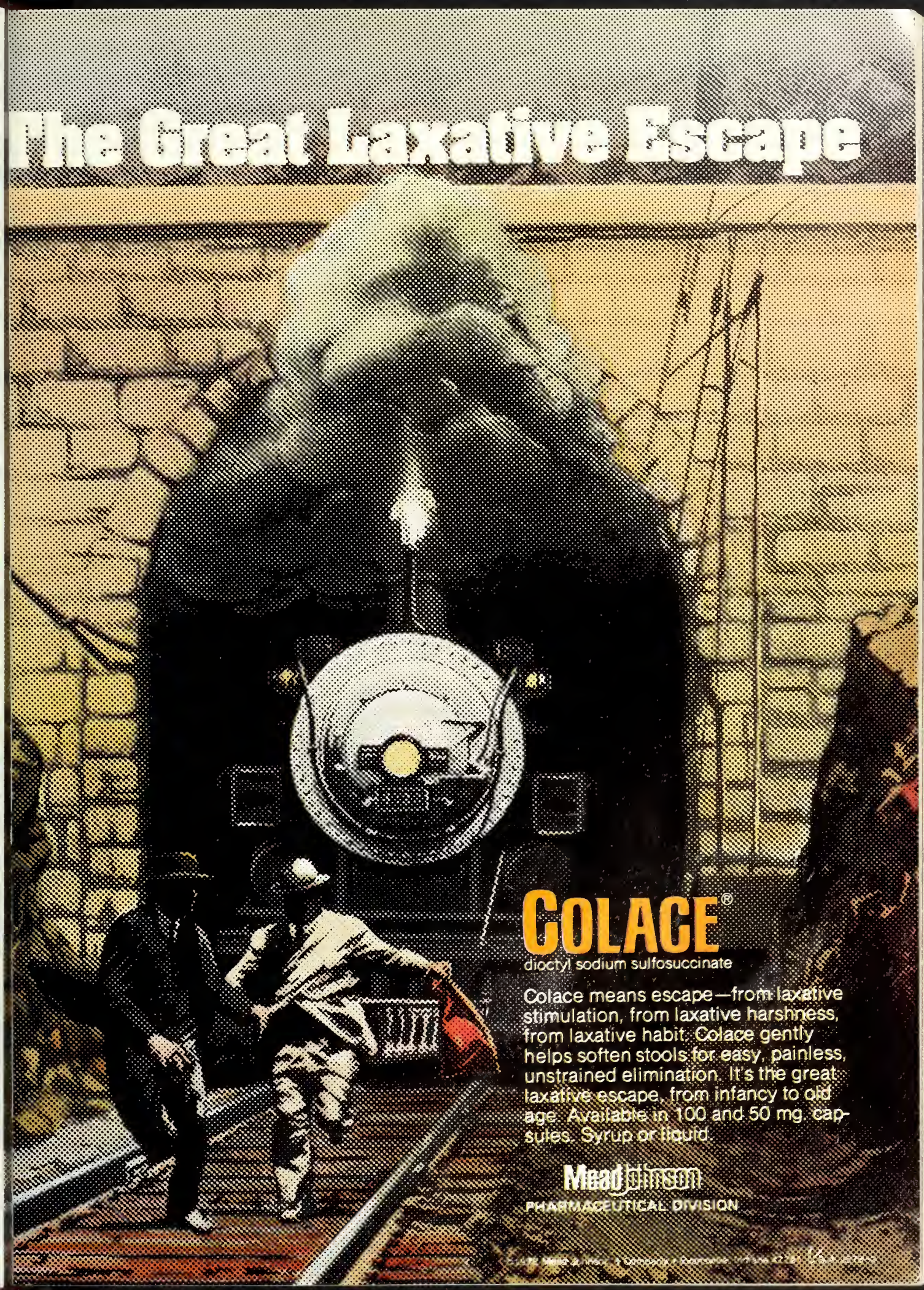
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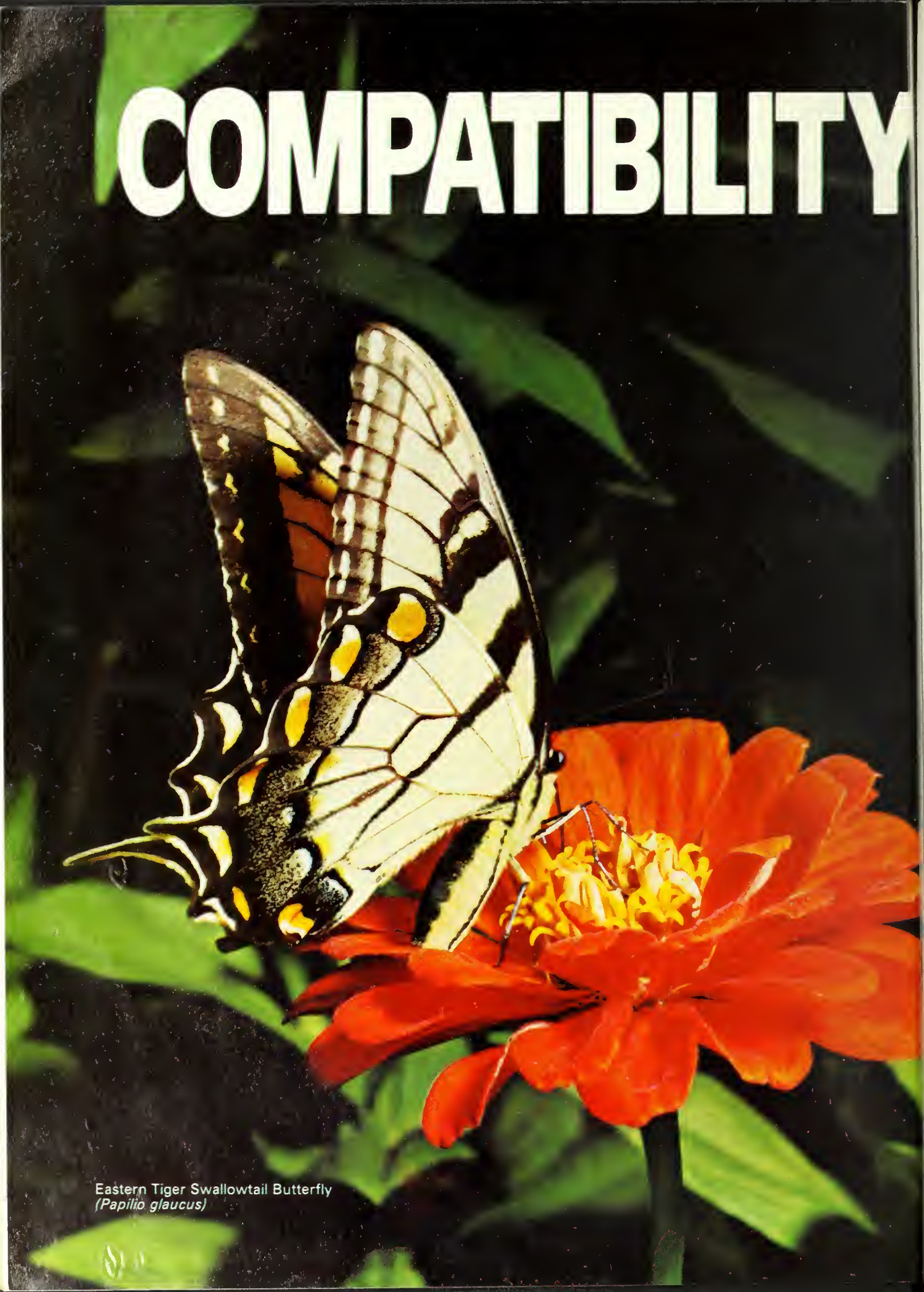

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Refer to: Einhorn LH, Williams SD: Chemotherapy of disseminated testicular cancer. West J Med 131:1-3, Jul 1979

Chemotherapy of Disseminated Testicular Cancer

LAWRENCE H. EINHORN, MD, *and* STEPHEN D. WILLIAMS, MD, *Indianapolis*

Dramatic improvements have been made in recent years in treatment of disseminated testicular cancer. Germ-cell neoplasms, even when advanced, are potentially curable by modern chemotherapy. Although disseminated testicular cancer is a rare disease, it is highly treatable, and primary physicians, internists and urologists should have some knowledge of its management.

In the 1960's dactinomycin alone or in combination with other drugs was the standard chemotherapy for testicular cancer. Complete disappearance of the disease occurred in about 15 percent of patients who received such treatment. Relapse would occur in about half of these patients, but the others would be cured.[1] Therefore, while the complete remission rate was relatively low with this therapy, the durability of remission was reasonably good.

In the late 1960's and early 1970's several new drugs effective in treating testicular cancer were introduced—vinblastine sulfate (Velban), bleomycin sulfate and mithramycin. These drugs, when used alone, have essentially the same degree of activity as dactinomycin. Of particular interest were vinblastine and bleomycin. The major toxic effect of vinblastine is myelosuppression, and that of bleomycin is pulmonary fibrosis. These drugs can be given in full dosage when used together. In addition, by virtue of their mechanisms of action, they appear to be synergistic. Results of studies at the University of Texas M. D. Anderson Hospital and Tumor Institute at Houston have shown that this regimen will produce complete responses in approximately 45 percent of patients.[2] Relapse occurred in only 33 percent, and many of these patients presumably are cured.

The newest active drug used to treat testicular cancer is Cis-diamminedichloroplatinum (DDP). It is probably the single most active agent. It is fairly toxic and the most notable problems are vomiting and nephrotoxicity; it almost never results in myelosuppression and, therefore, will combine well with vinblastine and bleomycin.

From August 1974 to September 1976, a total of 50 patients with disseminated testicular cancer were treated with DDP, vinblastine and bleomycin at Indiana University.[3] Table 1 outlines the treatment regimen. In 33 of 47 cases that could be evaluated, there was drug-induced disappearance of all disease. In five cases resection of residual tumor was done after almost total regression from chemotherapy. Recent analysis of these data shows that 33 of these patients are alive and 27 are without disease after from 21 to more than 45 months. Because most relapses of testicular cancer will occur within the first year, and practically all within two years, most if not all of these patients can be considered cured. These results are the best reported. Consequently we feel that optimal therapy for patients with metastatic testicular cancer is platinum-based combination chemotherapy.

Since September 1976 we have been evaluating the effects of lower dosages of vinblastine in an

From the Department of Medicine, Indiana University Medical Center, and Indianapolis Veterans Administration Medical Center.

Supported in part by Public Heath Service Grant No. MO1 RROO-750-06.

Submitted December 6, 1978.

Reprint requests to: Lawrence H. Einhorn, MD, Indiana University Medical Center, 1100 West Michigan Emerson Hall—435, Indianapolis, IN 46202.

TABLE 1.—*Treatment Regimen Used in 50 Patients at Indiana University, August 1974 to September 1976*

Remission Induction

- Cis-diamminedichloroplatinum (DDP), 20 mg per square meter given intravenously every day for five days
- Vinblastine sulfate (Velban), 0.2 mg per kg of body weight given in an intravenous push on days one and two of each course
- Bleomycin sulfate, 30 units given in an intravenous push six hours after Vinblastine on day two of each course and once a week for 12 weeks

Given every three weeks for three to four courses with continuous intravenous hydration

Maintenance

Vinblastine, 0.3 mg per kg of body weight, given every four weeks for a total of two years of therapy

attempt to reduce toxicity without lowering therapeutic efficacy. At present, it appears that equivalent results can be achieved by using a 25 percent reduction in dose (0.3 mg per kg of body weight) of vinblastine during remission induction.

Specific Aspects of Management

Markers

There is no other malignant condition in which tumor markers are as important as in testicular cancer. Most useful are assays of B-subunit chorionic gonadotropin (B-HCG) and α-fetoprotein (AFP). When measured by sensitive radioimmunoassay, elevations of one or both of these markers will occur in 90 percent of patients with active tumors. There are essentially no false positive findings and a patient with a history of testicular cancer who has an elevated marker must be considered to have an active tumor even if results of all other studies are normal and should be given appropriate treatment.[4] Moreover, in a patient with metastatic disease, the level of marker correlates well with the response to therapy, and markers must return to a normal level before the patient can be considered free from disease. It cannot be emphasized too strongly, however, that these tests must be done on serum by radioimmunoassay because other techniques are much too insensitive.

Side Effects of Chemotherapy

Aggressive combination chemotherapy for disseminated testicular cancer can be quite toxic, and such patients are best managed by trained medical oncologists. Alopecia, nausea, vomiting, paresthesias and constipation are troublesome but reversible side effects. Of major concern is myelosuppression, which is universal, particularly in patients who have had previous therapy with radiation. Consequently, if granulocytopenic fever develops, patients must be promptly admitted to hospital; cultures must be done, and broad-spectrum antibiotics—usually cephalosporin and carbenicillin—must be administered. Use of aminoglycoside antibiotics should be avoided because it may produce synergistic nephrotoxicity with DDP. DDP is potentially nephrotoxic and a variety of maneuvers have been used to ameliorate renal damage. In our experience, vigorous hydration with normal saline solution is sufficient. Physicians must be willing to carry out aggressive treatment and must be equipped to deal with toxicity because, ultimately, cure of these patients depends on such an approach.

Follow-up Examination

A major determinant of the prognosis in a particular case is the extent of disease at the time chemotherapy is begun. In patients with minimal metastatic disease there is a high probability (19 of 22 in our series) of complete remission occurring; consequently, careful follow-up examinations of all patients with testicular cancer is crucial. We obtain x-rays of the chest and assays of B-HCG and AFP every month for the first year in every patient, and every other month for the second year after surgical operation for localized disease or chemotherapy for disseminated disease. Therefore, recurrent disease can be diagnosed early, at a time when chemotherapy is most likely curative.

Integrated Management of Local Disease

Most patients with testicular cancer present initially with disease localized to the testis or to testis and retroperitoneal nodes. Diagnosis is confirmed on inguinal orchiectomy. Patients with pure seminoma ordinarily are treated with radiotherapy and there is an extremely high probability of cure. However, the approach in cases of nonseminomatous neoplasms (embryonal, teratoma or choriocarcinoma, or mixtures) is considerably different. If there is disease present outside the testis and draining lymphatics (usually shown as pulmonary metastatic lesions) the first approach should be platinum-based combination chemotherapy.

However, if results of thorough examination, including tomograms of the whole lung, show no

supradiaphragmatic disease, we favor proceeding with radical bilateral retroperitoneal lymph node dissection. If the nodes are normal, therapy is completed and there is a high probability of cure. As mentioned previously, however, careful follow-up examination, with x-ray studies of the chest and assays of B-HCG and AFP, is required.

There is considerably more controversy about proper management of abnormal retroperitoneal nodes. Many clinicians use preoperative or postoperative radiation therapy, or both, in this situation.[5,6] However, urologists who use surgical therapy alone seem to have equivalent results.[7,8] Whatever form of therapy is used, in about half of the patients relapse will occur and systemic therapy will be required. In our experience, there has been poor tolerance of chemotherapy and a lower rate of complete remission in patients in whom irradiation has been done. We do not use radiotherapy, therefore, in these cases.

We are frequently asked our opinion of the role of adjuvant chemotherapy in patients in whom findings are positive on resection of retroperitoneal nodes. A number of these patients are cured by surgical operation alone. Of the patients in whom relapse occurs, a sizable number will be cured by chemotherapy, particularly if the relapse is diagnosed early. Consequently, the usefulness of adjuvant therapy is open to question and answers can only be determined by a well-designed, controlled clinical trial. Such a study is now in progress.

Conclusions

Disseminated testicular cancer is a highly treatable disease and approximately half of all patients can be cured with chemotherapy. The treatment is vigorous and requires the services of experienced physicians. In all phases of the disease regular follow-up examinations consisting of x-rays of the chest and tumor marker studies should be done. Chemotherapy may be useful as adjuvant treatment, but a controlled clinical trial is required to define its usefulness.

REFERENCES

1. Ansfield FJ, Korbitz BC, Davis HC, et al: Triple drug therapy in testicular tumors. Cancer 24:442-446, 1969

2. Samuels ML, Lanzotti VJ, Holoye PY, et al: Combination chemotherapy in germinal cell tumors. Cancer Treat Rep 3:185-204, 1976

3. Einhorn LH, Donohue JP: Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. Ann Intern Med 87:293-298, 1977

4. Lange PH, Fraley EE: Serum alpha-fetoprotein and human chorionic gonadotropin in the treatment of patients with testicular tumors. Urol Clin North Am 4:393-406, 1977

5. Tyrell CJ, Peckham MJ: The response of lymph node metastases of testicular teratoma to radiation therapy. Br J Urol 48: 363-370, 1976

6. Maier JG, Mittemeyer B: Carcinoma of the testis. Cancer 39:981-986, 1977

7. Donohue JP: Retroperitoneal lymphadenectomy. Urol Clin North Am 4:509-521, 1977

8. Staubitz WJ, Early KS, Magoss IV, et al: Surgical management of testis tumor. Urology 111:205-209, 1974

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Fiberoptic Bronchoscopy in Diagnosis of Opportunistic Lung Infections

Assessment of Sputa, Washings, Brushings and Biopsy Specimens

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Fiberoptic bronchoscopy (washings, brushings and biopsies) was done in 25 cases of proven opportunistic pulmonary infections in compromised hosts. Diagnostic yields of bronchoscopic procedures and expectorated sputum were compared. Sputum examination gave the lowest yield (14 percent). Bronchial washings and brushings were diagnostic in 30 percent and 38 percent of patients, respectively. On transbronchial biopsy of the lung (TBB) pathogens were identified in 75 percent of patients with Pneumocystis carinii infection and 67 percent of patients with other opportunistic infections. The overall TBB yield of 73 percent was superior ($P<0.05$) to that of either washings or brushings. The yield from combining washings and brushings was greater than from either procedure alone, but combination with TBB did not result in any significant improvement. TBB is recommended as a useful diagnostic procedure in patients with suspected opportunistic pulmonary infections. Morbidity was minimal with this procedure, and the need for thoracotomy was reduced when it was used.

FIBEROPTIC BRONCHOSCOPY (FOB) with brushing and biopsy technique has been used for more than ten years principally for evaluating potentially neoplastic pulmonary lesions.[1-3] Little is known about the diagnostic usefulness of FOB for identifying opportunistic pulmonary pathogens in compromised hosts.[4,5] This report analyzes the usefulness of endobronchial brushings, washings and biopsies in evaluating this type of disease.

Patients and Methods

Case records of all immunocompromised patients who had FOB at the Center for the Health Sciences at the University of California, Los Angeles, from July 1975 through February 1978 were studied. A diagnosis of pulmonary disease due to opportunistic pathogens was confirmed in 25 cases by cultures of either lung aspirates and material obtained by needle aspiration, or open lung biopsy or autopsy, or both.

Before bronchoscopy, two or three specimens of sputa were obtained. The presence of polymorphonuclear leukocytes and histiocytes in a specimen indicated that it was sputum and not saliva.

Fiberoptic bronchoscopy was done using local cocaine (3 percent) for anesthesia. Details of our technique of examination have been described elsewhere.[1,6] Transbronchial biopsy was not done in patients in whom significant endobronchial

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bleeding occurred after brushings, or in those with bleeding diathesis.

All diagnoses of Pneumocystis carinii pneumonia were made by examining material from bronchial secretions, from lung biopsy specimens or from autopsy specimens stained with Gomori silver methenamine nitrate. A diagnosis of cytomegalic viral infection was based on culture of lung tissue obtained by biopsy or at autopsy. A diagnosis of fungal infection was based on culture of organisms obtained by transtracheal aspiration, FOB, biopsy of the lung or autopsy. Mycobacterium intracellularis infection was diagnosed by growth of the organism from bronchial washings and brushings on Löwenstein-Jensen (plain or modified) medium.

Statistical analysis was done by the chi square method using the Yates correction factor ($P \leq 0.05$).

TABLE 1.—*Types and Incidence of Infections*

Infection	*Number of Cases*
Pneumocystis carinii	10
Nocardia asteroides	2
Cytomegalovirus	3
Aspergillus fumigatus	4
Cryptococcus neoformans	2
Rhizopus oryzae	1
Blastomycosis dermatitidis	1
Mycobacterium intracellularis	1
Propionibacterium acne	1
Total	25

Results

Table 1 lists the pathogens isolated from these patients. Table 2 lists the clinical diagnoses, radiographic findings and diagnostic yields of FOB of ten patients with proven Pneumocystis carinii infection of the lungs. All were immunocompromised following chemotherapy for leukemia or Hodgkin disease, or steroid treatment for aplastic anemia, vasculitis or bone marrow transplantation. They presented with either diffuse (n=8) or localized (n=2) infiltrates on radiographic examination of the chest. Prebronchoscopy sputa were not useful. The yield of bronchial washings was 12 percent, brushings yielded 60 percent and transbronchial biopsy of the lung (TBB) yielded 75 percent.

Table 3 lists clinical presentations, radiographic findings and diagnostic yields from FOB of 15 patients with other opportunistic lung infections. The radiographic presentation again varied from localized to diffuse pulmonary involvement. Sputa obtained before bronchoscopy were diagnostic in 20 percent (Nocardia asteroides in two patients and Cryptococcus neoformans in one patient), bronchial washings in 6 of 15 (40 percent), brushings in 3 of 14 (21 percent) and TBB in 2 of 3 (67 percent) patients.

Table 4 lists the diagnostic yield from various types of specimens alone and in combination from all 25 patients with proven opportunistic pulmonary infections. The yield from sputa was

TABLE 2.—*Pneumocystis carinii Infection: Diagnoses and Role of Fibroptic Bronchoscopy in Diagnosis*

No.	*Age*	*Sex*	*Clinical Diagnosis*	*Findings on X-ray Studies of Chest*	*Sputa*	*Bronchoscopic Modalities*			*Other Diagnostic Techniques*
						Washings	*Brushings*	*Trans-bronchial Biopsy*	
1	32	M	Stem cell leukemia on ct	Diffuse infiltrates	−	−	−	−	Open lung biopsy (+)
2	19	M	ALL on ct	Diffuse infiltrates	−	N.D.	+	+	.....
3	43	M	Hodgkin disease on ct	Bilat. perihilar infiltrates	−	−	−	+	Autopsy (+)
4	46	M	Ankylosing Spondylitis on ct	Bilat. interstitial reticular nodular infiltrates	−	−	+	N.D.	.....
5	35	F	Hodgkin disease on ct	Consolidation right lung	−	−	+	+	Needle aspirate (+)
6	26	F	ALL on ct	Bilat. nodular infiltrates	−	−	−	−	Open lung biopsy (+)
7	34	F	Aplastic anemia on steroids	Bilat. diffuse reticular infiltrates	−	−	+	+	.....
8	78	M	Vasculitis on steroids	Right upper lobe consolidation	N.D.	−	+	N.D.	.....
9	30	F	S/P bone marrow transplant	Diffuse infiltrates	N.D.	+	+	+	.....
10	17	M	ALL on ct	Diffuse infiltrates	N.D.	N.D.	−	+	.....
					0/7 =0%	1/8 =12%	6/10 =60%	6/8 =75%	

+ = Diagnostic of Pneumocystis carinii
− = nondiagnostic
ALL = acute lymphocytic leukemia
ct = chemotherapy
N.D. = not done
S/P = status post

not greatly different from that of washings or brushings ($P>0.05$). However, the yield from a combination of washings and brushings was better ($P<0.05$) than the from sputa. The yield from TBB was much greater ($P<0.05$) than that from sputa, washings or brushings. The yield from combining washings or brushings with TBB was not notably greater than that from TBB alone. The yield from FOB was 57 percent in patients in whom TBB was *not* done, and 73 percent in patients in whom TBB was done.

Discussion

Pulmonary infection in immunocompromised patients is a difficult problem. To plan an appropriate antimicrobial regimen the etiological agent usually must be isolated as soon as possible. Many techniques have been used to diagnose pulmonary infiltrates in immunocompromised hosts, including percutaneous biopsy of the lung, transtracheal aspiration and fiberoptic bronchoscopic techniques.[4,7-9] However, to our knowledge no study comparing examinations of pulmonary secretions and lung biopsy specimens obtained during FOB for identifying opportunistic pulmonary secretions has been reported previously. We, therefore, analyzed the usefulness of sputa examination, bronchial washings, brushings and biopsies for diagnosis in this situation.

The pulmonary infections in our patients were similar to those reported in a comparable population surveyed at the National Institutes of Health,[10] where the most common cause of diffuse pulmonary infiltrates was Pneumocystis carinii. In one patient with lymphoma and hypogammaglobulinemia, Propionibacterium acne infection developed, causing necrotizing pneumonia with multiple pulmonary microabscesses. TBB

TABLE 3.—*Other Opportunistic Infections: Clinical Diagnoses and Role of Fiberoptic Bronchoscopy in Diagnosis*

						Bronchoscopic Modalities				
No.	*Age*	*Sex*	*Clinical Diagnosis*	*Findings on X-ray Studies of Chest*	*Sputa*	*Washings*	*Brushings*	*Trans-bronchial Biopsy*	*Other Diagnostic Techniques*	*Final Pulmonary Diagnosis*
11	36	M	Chronic renal failure Consolidation	Rt. lower lobe	+	−	−	N.D.	Needle aspiration	Nocardiosis
12	42	F	Chronic renal failure	Lt. lower lobe consolidation	−	−	−	+	.....	Phycomycosis
13	41	F	S/P mastectomy on ct and steroids	Unilateral infiltrates	+	+	−	N.D.	.....	Nocardiosis
14	24	M	AML on ct	Bilat. basal infiltrates	−	−	−	N.D.	Open lung biopsy	Cytomegalovirus (CMV) infection
15	19	M	AML on ct	Bilat. diffuse infiltrates	−	+	+	N.D.	Autopsy	CMV infection
16	25	M	AML on ct	Bilat. diffuse infiltrates	−	−	−	N.D.	Open lung biopsy	CMV infection
17	39	M	Chronic alcoholism	Perihilar infiltrates	−	−	−	+	.....	Cryptococcosis
18	37	M	Aplastic anemia	Unilateral infiltrates	−	−	−	N.D.	Open lung biopsy	Invasive aspergillosis and mycetoma
19	30	M	Pneumonia	Unilateral infiltrates	−	+	N.D.	N.D.	.....	Aspergillosis
20	50	M	Lung tumor	Lingular infiltrates	+	+	+	N.D.	.....	Cryptococcosis
21	72	F	Chronic granulomatous lung disease	Bilat. diffuse infiltrates	−	+	+	N.D.	.....	Mycobacterium intracellularis infection
22	36	M	Aplastic anemia	Perihilar infiltrates	−	+	−	N.D.	.....	North American blastomycosis
23	34	M	S/P bone marrow transplant	Perihilar infiltrates	−	−	−	N.D.	Autopsy	Disseminated aspergillosis
24	65	M	Lymphocytic lymphoma	Bilat. basilar infiltrates	−	−	−	−	Open lung biopsy	Propionibacterium acne
25	39	M	AML on ct	Bilat. diffuse infiltrates	−	−	−	N.D.	Autopsy	Diffuse aspergillosis
					3/15 =20%	6/15 =40%	3/14 =21%	2/3 =67%		

+ = Diagnostic
− = nondiagnostic
AML = acute myelocytic leukemia
ct = chemotherapy
N.D. = not done
S/P = status post

was not diagnostic in this case and the diagnosis was made by open lung biopsy. Organisms were seen on Gram stain and anaerobic culture yielded pure isolates of Propionibacterium acne. This pathogen had not been isolated in previous studies[4,5] and incidence of this infection in lungs of immunocompromised patients is not known. Cases in which Candida albicans was grown on culture of material obtained during FOB were excluded from analyses of the data. This was done because previous studies reported the isolation of Candida organisms from 20 percent of lung tissue specimens obtained at biopsy or surgical operation in patients with chronic lung disease that was not due to Candida organisms.[11] Also, Candida organisms have been grown on culture of lung tissue specimens obtained at autopsy in cases without antecedent clinical disease or histologic evidence of tissue invasion.[12] Reliable information about possible Candida infection of the lung, therefore, cannot be obtained by FOB.

It has been reported that expectorated sputum yields Pneumocystis carinii organisms occasionally in cases of interstitial pneumonitis.[13] In our study sputum examination was not useful. However, Nocardia asteroides were isolated from sputum in two cases and Cryptococcus neoformans were found in one case. These organisms were also isolated from secretions obtained at FOB. The overall diagnostic yield of sputum examination was low (14 percent) and not cost-effective.

Most authors favor the use of open lung biopsy to diagnose Pneumocystis carinii infection. With this procedure sufficient material can usually be obtained to assess the relative contributions of two or more concommitant disease processes. However, the yield is nearly as high with TBB, a much less invasive procedure, which established the diagnosis of Pneumocystis carinii infection in six of eight patients (75 percent) in our series. Others have found similar results with TBB in immunocompromised hosts.[14-16] Among all infections, the yield from TBB alone was 73 percent and with TBB along with brushings or washings, the yield was 65 percent to 75 percent. However, TBB was done in only three of 15 patients with infections from organisms other than Pneumocystis carinii. More data are needed to confirm the value of this procedure in diagnosing these infections. When TBB was not done the yield of FOB was 57 percent (Table 4). Therefore, TBB is the most important single bronchoscopic procedure for diagnosing these infections. However,

TABLE 4.—*Diagnostic Yield of Sputum Examination and Fiberoptic Bronchoscopy in 25 Patients*

Specimen	*Number of Cases*	*Diagnosis Established*	*Percent Yield*
Sputum	22	3	14
Washings	23	7	30
Brushings	24	9	38
Biopsy	11	8	73
Washing and brushings	22	10	45
Brushings and biopsy	11	8	73
Washings and biopsy	9	6	67
Washings and brushings and biopsy	9	6	67
Washings or brushings or biopsy	25	16	64

a possibility of associated second or third infections in these persons should be kept in mind and these may be missed in the tissue specimens obtained by TBB. Compared with brushings or washings, there were no false negative findings from TBB.

Major complications of TBB occurred only rarely in this group of patients. Significant endobronchial blood loss occurred in one. Pneumothorax requiring chest tube placement did not occur in this series. We conclude that FOB combined with TBB is a useful diagnostic procedure for determining the cause of opportunistic pulmonary infections in immunocompromised hosts, and that the need for thoracotomy is diminished when this procedure is available.

REFERENCES

1. Chopra SK, Genovesi MG, Simmons, DH, et al: Fiberoptic bronchoscopy in the diagnosis of lung cancer, comparison of pre- and post-bronchoscopy sputa, washings, brushings and biopsies. Acta Cytologica 21:524-527, 1977
2. Zavala DC: Diagnostic fiberoptic bronchoscopy. Chest 68: 12-19, 1975
3. Ikeda S, Yanai N, Ishikawa S: Flexible bronchofiberscope. Keio J Med 17:1-16, 1968
4. Finley R, Keiff E, Thomsen S, et al: Bronchial brushing in the diagnosis of pulmonary disease in patients at risk for opportunistic infection. Am Rev Resp Dis 109:379-387, 1974
5. Williams DM, Krick JA, Remington JS: Pulmonary infections in the compromised host. Am Rev Resp Dis 114:359-394, 1976
6. Chopra SK, Ben-Isaac FB: Transbronchial lung biopsy using fiberoptic bronchoscope. South Med J 70:302-304, 1977
7. Aisner J, Kvols LK, Sickles EA, et al: Transtracheal selective bronchial brushing for pulmonary infiltrates in patients with cancer. Chest 69:367-371, 1976
8. Anderson HA, Miller WF, Bernatz PE: Lung biopsy: Transbronchoscopic, percutaneous, open. Surg Clin North Am 53:785-793, 1973
9. Lau WK, Young LS, Remington JS: Pneumocystis carinii pneumonia—Diagnosis by examination of pulmonary secretions. JAMA 236:2399-2402, 1976
10. Goodell B, Jacobs JB, Powell RD, et al: Pneumocystis carinii: The spectrum of diffuse interstitial pneumonia in patients with neoplastic disease. Ann Intern Med 72:337-340, 1970
11. Kahanpaa A: Bronchopulmonary occurrence of fungi in adults, especially according to cultivation material. Acta Pathol Microbiol Scan (B) 227:1-147, 1972, p 1
12. Haley LD, McCabe A: A mycologic study of seventy-one autopsies. Am J Clin Pathology 20:35-38, 1950
13. Walzer PD, Perl DP, Krogstad DJ, et al: Pneumocystis carinii pneumonia in the United States: Epidemiologic, diagnostic and clinical features. Ann Intern Med 80:83-94, 1974
14. Pennngton JE, Feldman NT: Pulmonary infiltrates and fever in patients with hematologic malignancy: Assessment of transbronchial biopsy. Am J Med 62:581-587, 1977
15. Repsher LH, Schroter G, Hammond WS: Diagnosis of pneumocystis carinii pneumonitis by means of endobronchial brush biopsy. N Engl J Med 287:340-341, 1972
16. Feldman NT, Pennington JE, Ehrie MG: Transbronchial lung biopsy in the compromised host. JAMA 238:1377-1379, 1977

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High Altitude Medical Problems

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Increased travel to high altitude areas by mountaineers and nonclimbing tourists has emphasized the clinical problems associated with rapid ascent. Acute mountain sickness affects most sojourners at elevations above 10,000 feet. Symptoms are usually worse on the second or third day after arrival. Gradual ascent, spending one to three days at an intermediate altitude, and the use of acetazolamide (Diamox) will prevent or ameliorate symptoms in most instances. Serious and potentially fatal problems, such as high altitude pulmonary edema or cerebral edema, occur in approximately 0.5 percent to 1.0 percent of visitors to elevations above 10,000 feet—especially with heavy physical exertion on arrival, such as climbing or skiing. Early recognition, high flow oxygen therapy and prompt descent are crucially important in management. Our knowledge of the causes of these and other high altitude problems, such as retinal hemorrhage, systemic edema and pulmonary hypertension, is still incomplete. Even less is known of the effect of high altitudes on medical conditions common at sea level or on the action of commonly used drugs.

EXPOSURE TO HIGH ALTITUDE of people of all ages and degrees of health has enormously increased in the last ten years. Modern travel facilities and the advent of mountain tours and trekking safaris now permit access to high mountain regions previously visited only rarely by hardy climbers. In 1976 there were 671 climbers on Mount McKinley (20,320 feet) and each year more than 5,000 people climb Mount Rainier (14,408 feet). In the Himalayas during one four-week period in 1975 there was 522 trekkers who hiked up to Pheriche (14,000 feet) en route to the Everest base camp. In the Mount Kenya area 3,500 climbers and trekkers climb above 13,000 feet each year. Skiers in the Rocky Mountains are not immune to high altitude illness; many ski resorts are located at 8,000 feet or higher, with ski runs starting at 11,000 and 12,000 feet. Such resorts can be easily reached in one day from any part of the United States. High altitude pulmonary edema has been observed in hikers and skiers in the Sierra Nevadas, and helicopters now carry skiers to 12,500 feet from the eastern side of the Sierras. In South America large permanent populations live and work at altitudes as high as 16,500 feet. Physicians should be aware of common medical problems of acute and chronic high altitude exposure. For these reasons this review of

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ABBREVIATIONS USED IN TEXT

AMS=acute mountain sickness
HAPE=high altitude pulmonary edema

current concepts of high altitude illness has been prepared.

Definition of High Altitude

For the purpose of this review high altitude will refer to elevations of 8,000 to 15,000 feet above sea level. It is rare for symptoms of altitude illness to occur below 8,000 feet and few mountain tours or permanent human habitations extend above 15,000 feet.

Role of Hypoxia

It is apparent that the most important effect of high altitude exposure is hypoxia. At 12,000 feet the normal resting arterial oxygen saturation is 85 percent. At 15,000 feet the saturation falls to 78 percent. At 19,000 feet the arterial saturation is 69 percent. During exercise at sea level arterial oxygen saturation does not fall. However, during exercise at high altitude oxygen saturation falls due to limitations in maximal pulmonary diffusing capacity (Figure 1). At 15,000 feet the saturation may fall to 69 percent and at 19,000 feet heavy exercise may decrease arterial saturation to levels as low as 40 percent to 50 percent.[1-3] This is one factor that limits climbing performance at very high altitudes. In addition, during sleep at high altitude the drop in arterial saturation is considerably more than the slight decrease observed at sea level. Persons at 17,200 feet with an arterial oxygen saturation of 74 percent when awake have a mean saturation of 64 percent during sleep. With irregular respiration during sleep, saturations below 40 percent have been observed.[4]

While arterial carbon dioxide tension (P_{CO_2}) falls during high altitude exposure it is unlikely that hypocapnia is responsible for symptoms of altitude exposure.

Acute Mountain Sickness

Rapid exposure to high altitude of unacclimatized persons commonly results in a group of symptoms generally known as acute mountain sickness (AMS). Severe symptoms rarely occur below 8,000 feet and in most persons some symptoms will be present from 10,000 to 12,000 feet.

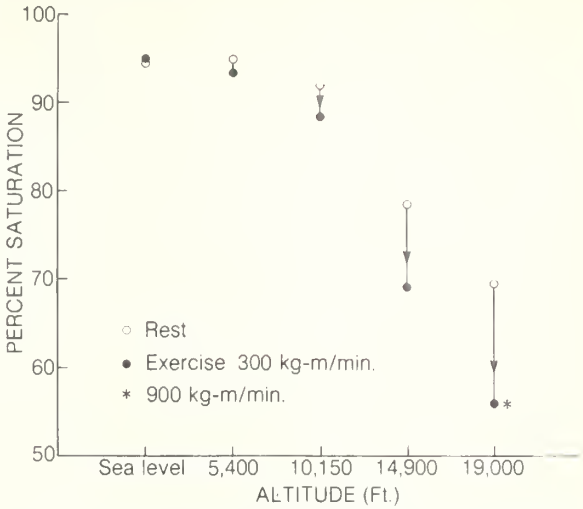

Figure 1.—Arterial oxygen saturation in normal man at sea level and various altitudes at rest and during moderate exercise. (Reprinted with permission from Banchero et al.[1])

AMS is the most common high altitude illness.

Excellent descriptions of AMS have been published by Acosta[5] and Barcroft.[6] Acosta's description is one of the earliest published records of AMS (1589). Barcroft's report describes symptoms affecting passengers on a train trip from Lima to Cerro de Pasco, Peru (14,200 feet). The most common initial symptom consists of headache, which may vary in severity from a mild feeling of lightheadedness or dizziness to severe, prolonged, incapacitating pain. Lassitude, anorexia, drowsiness, a general feeling of malaise, weakness and dyspnea on exertion are common. During ascent, somnolence, chilliness with pallor of the face, and cyanosis of the lips and nailbeds are frequently noted. Nausea and vomiting may occur, especially in children.

After arrival, a feeling of warmth and flushing of the face may be noted for the first 24 to 48 hours. The above symptoms may persist for several days, although in most instances they disappear within 24 to 48 hours. Sleep, especially for the first few nights, is difficult, with frequent periods of wakefulness and often strange dreams. Even slight physical effort may produce troublesome dyspnea, often requiring considerable rest until the respiratory distress has ceased. Weakness and palpitation on effort may be noted; tachycardia may be present. A common complaint is dull pain and discomfort in the the muscles of the posterolateral chest wall. Cheyne-Stokes respiration may be experienced above 8,000 feet and it occurs in nearly all persons at altitudes above

13,000 feet. It appears most frequently during the night and is a major factor in preventing sound, restful sleep. If present during the day, it does not appear to be related to activity or meals. It is rarely continuous, but appears and disappears, lasting for minutes to hours.

Neurologic and cerebral symptoms may be experienced, including a reduced capacity for sustained mental work, memory defects, auditory and visual disturbances, vertigo and tinnitus. Irritability may be noted. Appetite may remain poor; a weight loss of from 5 to 10 pounds may occur in adults. In some persons symptoms may persist throughout their stay at high altitudes and may result in their inability to work efficiently or, in some cases, may necessitate a return to sea level.

Headache is the most severe and disabling symptom of AMS. It has been suggested that headache is due to cerebral edema; however, cerebral edema in other clinical conditions is not regularly assocated with headache. A more plausible cause is spasm or dilatation of cerebral blood vessels related to hypocapnia (which causes cerebral vasoconstriction) or hypoxia (which causes cerebral vasodilatation).

AMS may not be evident during the first 24 hours of altitude exposure and the symptoms are usually most severe on the second and third day. Sleep at high altitude is more conducive to AMS and reinforces the wisdom of the climbers' strategy of "sleep low and climb high." On Mount Whitney (14,495 feet), for example, AMS occurs less frequently in climbers who make the ascent in one day from Owens Valley than in those who spend the night at Mirror Lake (10,640 feet).

Treatment

Mild or moderately severe AMS is best treated by rest, light diet, increased fluid intake and symptomatic measures to relieve headache (aspirin, codeine). Smoking and the use of alcohol should be avoided. Voluntary hyperventilation every 10 to 15 minutes may be helpful. Excessive hyperventilation may result in symptoms of acapnea including dizziness and tingling or numbness of the hands and lips. Barbituates may make rest and sleep possible, but may be associated with an intensification of symptoms upon awakening. For severe episodes descent or administration of oxygen are indicated. Continuous oxygen administration (1 to 2 liters per minute) with a plastic face mask during sleep may be very helpful, not only in the relief of symptoms but in facilitating restful sleep. Lightweight oxygen tanks are now available that provide 247 liters of oxygen with a variable flow regulator with a carrying weight of only 6½ pounds (Erie Manufacturing Co., 4000 S. 13th St., Milwaukee, Wisconsin 53221).

Prevention

The most effective method of preventing AMS is by acclimatization. This can be achieved by a sojourn at an intermediate altitude (6,000 to 8,000 feet) for two to four days before going to a higher altitude. Another effective measure is gradual ascent by climbing 1,000 feet per day interrupted by an occasional day of rest. In trekking parties to the Everest base camp AMS was seen far more frequently in those who flew from Katmandu to Lukla (9,240 feet) than in those who walked this distance over 13 days.[7] For those persons susceptible to AMS the administration of acetaxolamide (Diamox) may be helpful.[7-9] Acetazolamide may be given in a dose of 250 mg once or twice a day beginning on the day of ascent and continued for two to five days after arrival. Side effects such as tingling of the lips and finger tips, alteration in the taste of beer and myopia usually occur only if acetazolamide administration is continued for more than five days.[7,8] Field studies of troops have shown that AMS at 14,200 feet can be ameliorated by staging for four days at 5,300 feet and administering acetazolamide (500 mg twice a day) for the last two days of staging and the first two days at high altitude. Treated persons at high altitude had a higher arterial oxygen tension, a lower arterial carbon dioxide tension and a lower pH than control subjects.[8] The dosage of acetazolamide in these studies was high, usually 250 mg twice a day. A higher staging altitude of 6,000 to 7,000 feet may be preferable.

Furosemide (Lasix) is of no value in preventing AMS. Physical conditioning before ascent does not appear to reduce the incidence or severity of AMS but it will permit more effective climbing. Alkalinization of the blood by the use of antacids is of no value. Even the ingestion of 50 grams of sodium bicarbonate per day for three days resulted in no major effect upon the respiratory response to hypoxia.[10]

Subacute Mountain Sickness

Symptoms of AMS disappear in two to six days. In rare instances symptoms may persist for weeks or months. Major problems may consist of ano-

rexia with weight loss, insomnia, and mental and physical fatigue. Symptoms will disappear upon descent to a lower altitude.

Chronic Mountain Sickness

Chronic mountain sickness is a rare condition seen only in people who have lived for months or years at high altitudes. Weakness, fatigue, somnolence and mental confusion are common symptoms. Physical findings consist of pronounced cyanosis and plethora with, occasionally, clubbing of the fingers and toes. Signs of pulmonary hypertension are present. Arterial oxygen saturation is low and notable polycythemia is present with hematocrit readings as high as 80 percent being occasionally observed. Right ventricular failure may occur and cause death. Symptoms and signs disappear upon return to a lower altitude. Alveolar hypoventilation due to a diminished respiratory response to hypoxia is the probable cause.[11,12]

Chronic Mountain Polycythemia

In persons living permanently at high altitudes, hematocrit readings may occasionally be high without symptoms or signs of chronic mountain sickness. At 12,000 feet the normal hematocrit reading is 54 percent and at 14,900 feet it is 58 percent. However, occasionally values of 60 perpercent to 70 percent may occur in evidently healthy persons living at high altitudes. The excessive polycythemia that occurs is probably due to decreases in arterial oxygen saturation during sleep, which is more severe in polycythemic persons than in normal persons. All night mean arterial saturation in five polycythemic subjects was 79 percent compared with 88 percent for five normal subjects studied by Kryger and his associates at 10,152 feet in Leadville, Colorado.[13]

Pulmonary Hypertension of High Altitude

A moderate increase in pulmonary artery pressure and pulmonary arteriolar (precapillary) resistance is present in people living at high altitudes. At 12,000 feet and 14,900 feet the normal mean pulmonary artery pressure is 22 mm and 30 mm, respectively (compared with the normal sea level value of 14 mm of mercury). In occasional instances, particularly in children, high pulmonary artery pressures may be encountered without symptoms. Signs of pulmonary hypertension may be shown on physical examination, x-ray studies of the chest and electrocardiograms. The subjects are usually asymptomatic and signs of right ventricular failure are absent. Pulmonary artery pressures will return to normal upon return to sea level.[14,15] This condition appears to be benign with an excellent prognosis. Continued residence at high altitudes does not appear to be harmful. Increased pulmonary vasoconstriction due to hypoxia (pulmonary vascular hyperreactivity?) is the probable cause. The condition should not be confused with the sea level disorder of primary pulmonary hypertension, which has a poor prognosis.

High Altitude Pulmonary Edema

General

High altitude pulmonary edema (HAPE) occurs in unacclimatized persons who are rapidly exposed to altitudes greater than 8,000 feet. It is most frequently seen in climbers who ascend to high altitudes without previous acclimatization and who engage in heavy physical exertion on arrival. Initial symptoms of dyspnea, cough, fatigue and occasionally hemoptysis appear, usually within two to seven days after arrival. Common physical signs are tachypnea, tachycardia, rales, cyanosis and hypotension. In severe episodes there may be disturbances of consciousness or coma. Descent to a lower altitude, bed rest and oxygen administration result in rapid clinical improvement. Fatal episodes continue to occur in many parts of the world as access to high altitudes by unacclimatized visitors is facilitated by modern means of travel. Most deaths occur when a prompt diagnosis is not made, when the victim is not moved to a lower altitude or when oxygen is unavailable. Preexisting cardiac or pulmonary disease has not been shown to be a factor in the development of HAPE. Physiologic studies during the acute stage in patients have shown normal pulmonary artery wedge pressure, pronounced elevation of pulmonary artery pressure, severe arterial unsaturation and usually low cardiac output. Pulmonary arteriolar (precapillary) resistance is elevated. The incidence is higher in adolescents but may occur at any age. HAPE represents one of several varieties of acute pulmonary edema in which left ventricular filling pressure is normal.

Clinical Presentation

The first symptoms of HAPE usually begin 24 to 96 hours after arrival at high altitude and are commonly preceded by heavy physical exertion such as climbing, skiing or carrying heavy loads. Dyspnea, a persistent nonproductive cough, and notable weakness and fatigue are the most com-

mon early symptoms. Headache, nausea, vomiting or somnolence is often seen in children. As the severity of the pulmonary edema increases, usually during the night, dyspnea at rest becomes severe and the cough becomes productive of clear, copious watery sputum. Rhonchi and gurgling sounds can be heard without a stethoscope. Hemoptysis, sometimes involving fairly large quantities of blood, can be seen in about 20 percent of severe episodes. A typical patient becomes apprehensive, fears death, and may become incoherent or irrational or experience hallucinations. Coma may follow and precedes death by 6 to 12 hours if oxygen is not administered or the patient is not carried to a lower altitude. In rare instances, stupor progressing to coma may occur, with minimal symptoms or signs of respiratory distress, and the clinical features may resemble those of encephalitis or intracranial disease.[16,17] Central nervous system dysfunction and altered consciousness are probably related to hypoxia or cerebral edema, which may be profound in severe HAPE.[16]

Common clinical signs include cyanosis, hyperpnea, crepitant rales and rhonchi. The blood pressure is low. In a study of 21 patients in Peru, the mean arterial pressure was 106/69 mm of mercury. Tachycardia due to severe hypoxia is present, with heart rates up to 160 per minute in severe episodes. The mean heart rate in 34 Peruvian episodes was 122 per minute. The respiratory rate is increased and a mean value of 32 per minute was observed in Peruvian studies.[18]

Laboratory Studies

Laboratory studies in persons with high altitude pulmonary edema show elevated hematocrit reading and acid urine with high specific gravity

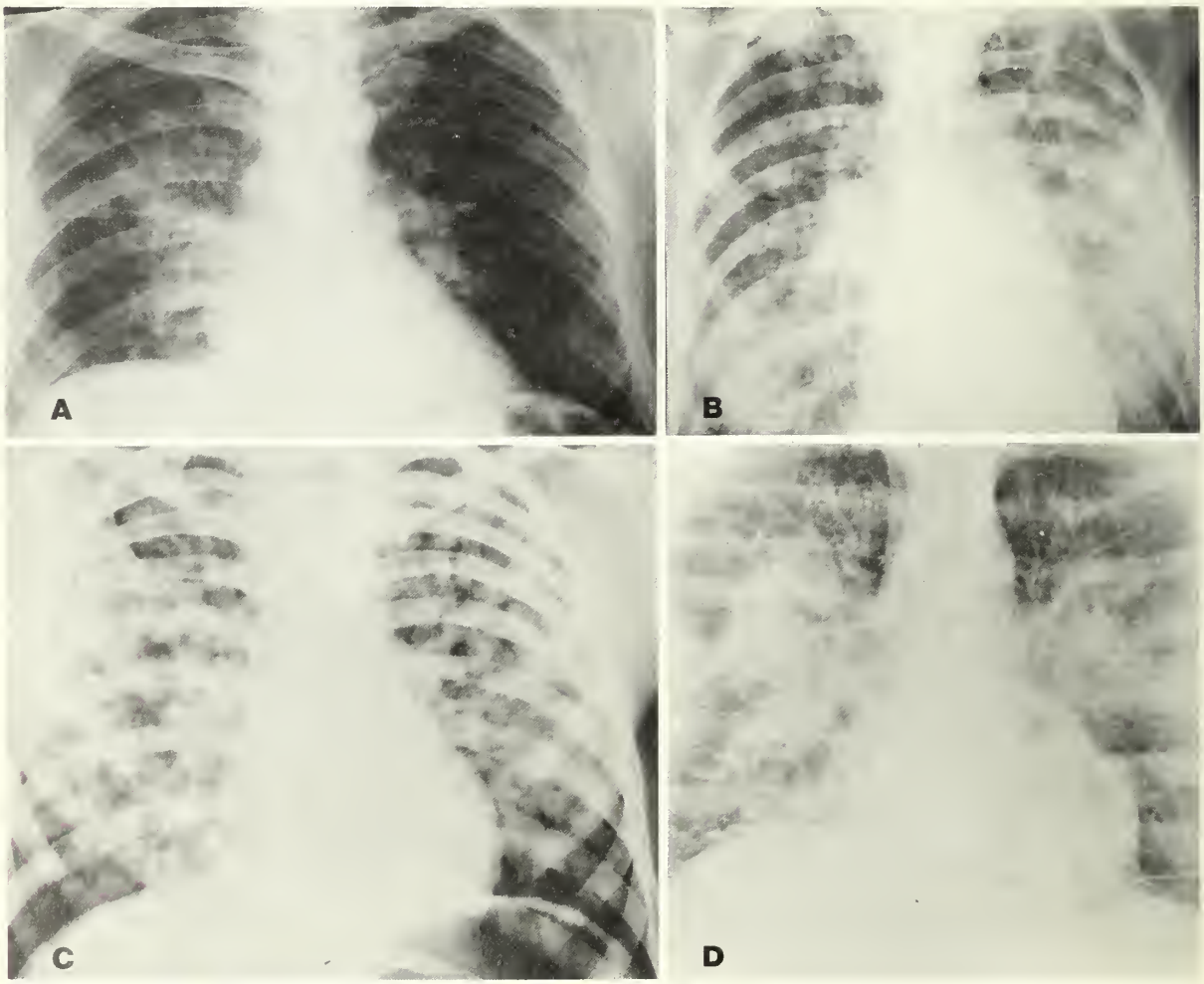

Figure 2.—A, Mild high altitude pulmonary edema (HAPE) occurring in a hiker in the Sierra Nevadas. **B,** HAPE of moderate severity in a 14-year-old boy at 14,200 feet. **C,** Severe HAPE in a young boy at 12,500 feet. **D,** Cardiac pulmonary edema due to acute chordal rupture with mitral regurgitation.

compatible with hemoconcentration. Signs of infection are absent, with only minor temperature elevation, a normal or moderately raised leukocyte count and a normal sedimentation rate.

Electrocardiograms during acute HAPE show tachycardia and signs of acute right ventricular overload, including right axis deviation, P-wave abnormalities compatible with right atrial strain, prominent R waves in the right precordial leads, and S waves in leads V_5 and V_6. In one instance transient atrial flutter has been noted. The changes are similar to those occurring during pulmonary embolism and acute cardiac pulmonary edema and subside during treatment. The electrocardiographic abnormalities are probably due to acute pulmonary hypertension.

Radiologic Features

Radiologic studies have been done in many instances of HAPE and the extent of the edema shown on films of the chest roughly parallels the clinical severity. In mild episodes, single or several small patchy infiltrates are present. In severe forms the infiltrates may nearly fill both lung fields. The infiltrates are rarely confluent and clear spaces of aerated lung are usually present especially at the lung bases. The edema is more severe and common in the right mid-lung field. The usual symmetrical, *bat-wing,* distribution of edema commonly seen in cardiac pulmonary edema or uremia is rare. The central branches of the pulmonary artery are prominent but the overall heart size is not increased. Left atrial enlargement and pulmonary venous congestion are absent. Kerley lines of pulmonary venous hypertension are absent. Pleural effusion is rare.

Serial x-ray films of the chest during recovery from HAPE show clearing of infiltrates and decrease in prominence of the pulmonary arteries, but no consistent change in heart size.[18] The radiologic features of HAPE are illustrated in Figure 2.

In persons with severe HAPE, especially when treatment has been delayed or recovery is slow, infiltrates persisting for many days, or even up to two weeks after clinical recovery, may be noted on x-ray films of the chest.[19] For this reason it is advisable that such studies be done on any person who may have had an episode of HAPE, even though clinical recovery has occurred. Films showing a slowly clearing residual pulmonary infiltrate may confirm, therefore, the diagnosis of suspected HAPE even after return to sea level.

Severity

In evaluating treatment and prognosis, objective assessment of the severity of HAPE is important. In an evaluating therapy for HAPE in Peru,[20] a simple method of grading severity has been used based on clinical features, echocardiographic findings and x-ray films of the chest (see Table 1). General experience indicates that patients with grade 4 severity usually die unless prompt therapy can be instituted.

The mortality of HAPE is variable and depends on many factors. Studies of large population groups at risk indicate a mortality of 0.5 percent to 12.7 percent.[21,22]

Incidence and Age

A study of the incidence of HAPE has been carried out in the mining town of La Oroya (altitude 12,300 feet) in the central Peruvian Andes.[23] Many permanent residents live in this community

TABLE 1.—*Classification of the Severity of HAPE*

*Grade**	*Clinical*	*Electrocardiogram*	*X-ray Film of the Chest*
1 Mild	Minor symptoms with dyspnea only on heavy exertion	Tachycardia only; heart rate at rest <110	Minor exudate involving less than a fourth of one lung field
2 Moderate ...	Symptoms of dyspnea, weakness, fatigue on ordinary effort; headache, dry cough	Tachycardia with resting heart rate 110-120; P wave changes only	Exudate involving at least half of one lung field
3 Serious	Symptoms of dyspnea, headache, weakness, nausea at rest; loose recurrent productive cough	Tachycardia with heart rate 120-140; P wave and minor QRS-T wave changes	Bilateral exudates involving at least half of each lung field
4 Severe	Stupor or coma; inability to stand or walk; severe cyanosis; bubbling rales present with copious sputum, usually bloody	Tachycardia with heart rate >140; right axis deviation, QRS, T wave and P wave changes	Bilateral exudates involving more than half of each lung field

HAPE = high altitude pulmonary edema

*Grades 1 and 2 can usually be treated with bed rest alone without descent. Grade 4 is usually fatal unless immediate descent and oxygen treatment can be carried out.

and make frequent trips to sea level for vacations or business purposes. Questionnaires were sent to families living in the area asking for details about altitude exposure, trips to sea level and occurrence of HAPE in their families during the preceding year. A total of 860 exposures to high altitude in 95 persons was reported. An exposure was defined as a rapid ascent to 12,300 feet or higher from sea level either for the first time or after a sea level visit of greater than two weeks. The overall incidence of HAPE during 860 exposures to high altitude was 3.4 percent. It occurred in two of 50 adults (4 percent) and in 17 of 45 subjects younger than 21 (38 percent). No cases affecting children less than 2 years old occurred. Three of the younger group had a total of nine repeat episodes of HAPE. For a single ascent, the estimated chance of HAPE is 6 percent for persons less than 21 years old and 0.4 percent for persons older than 21.

The incidence in Indian troops transported by air to altitudes above 11,500 feet was 5.7 percent in another study. If travel was by automobile, the incidence was 0.3 percent. About half the patients were between 20 and 29 years old.[22] Singh has reported an incidence of 13 percent to 15 percent in troops moved rapidly to altitudes of 11,000 to 18,000 feet.[21] The incidence was similar for men going to high altitudes for the first time and those who were returning from a furlough at lower altitudes.

Previous studies from Peru have also shown a high incidence of HAPE in children and adolescents compared with adults.[18] The characteristics of HAPE occurring in children have been described.[24,25] The incidence of HAPE in women is low, but for children there is no sex dominance.[18] Studies in Leadville, Colorado, (10,150 feet) have also shown a higher incidence of HAPE in children.[26]

Subclinical HAPE

The data described refer only to obvious HAPE severe enough to require medical attention. If one includes subclinical HAPE, the true incidence will be substantially higher than indicated. Houston has made observations of climbers before and after an ascent to Mount Rainier, Washington (14,408 feet). Of 140 subjects, 15 percent had pulmonary rales after descent, suggesting the presence of mild pulmonary edema.[16] Singh noted that about a third of patients with severe acute mountain sickness had pulmonary rales.[21] Subclinical pulmonary edema, therefore, can be estimated to occur at least three times as frequently as the more severe form.

Altitude of Occurrence and Acclimatization

High altitude pulmonary edema rarely occurs below 8,000 feet and the incidence increases with altitude. Episodes occurring between 8,000 and 10,000 feet are usually related to heavy physical exertion, but at higher altitudes pulmonary edema occurs with only light activity or even at rest. HAPE rarely develops in persons who are acclimatized for one to two weeks except at very high altitudes. At the Mount Everest base camp in 1963, several thoroughly acclimatized members of the party had clinical signs of mild pulmonary edema after strenuous climbing during the day. These signs disappeared after bed rest and low-flow oxygen administration during the night. HAPE is rare in fully acclimatized residents of high altitude regions unless there is rapid ascent to a higher altitude.

HAPE During Reascent

In fully acclimatized persons who descend to sea level and then return to high altitude, HAPE may develop on reascent. HAPE during reascent is rare when the sea-level sojourn is less than 10 to 14 days,[18,21,22] Pulmonary edema during reascent may occur more frequently than pulmonary edema during initial ascent to high altitudes,[20] but further data are needed to settle this point.

Susceptible Persons

Some persons seem to be susceptible to HAPE and may have recurrent episodes when again ascending to high altitude.[18,23] In the study in La Oroya, Peru, 20 percent of patients with HAPE had experienced at least one previous episode.[23] Physiologic studies have indicated that in persons with a history of HAPE there are an abnormal rise in pulmonary arteriolar resistance and an impaired oxygen exchange during acute altitude exposure that are not observed in normal subjects.[16] In susceptible persons there is also a more pronounced rise in pulmonary artery pressure and arteriolar resistance than in normal persons during low oxygen breathing.[27-29]

Treatment

Prompt recognition of the syndrome, bed rest, descent to a lower altitude and oxygen adminis-

tration are the most effective methods of therapy for HAPE.[20,30]

Recognition

Severe HAPE and many fatalities among mountain climbers have occurred because initial symptoms have been ignored or concealed, or because pneumonia has been incorrectly diagnosed. Recognizing early symptoms permits prompt initiation of therapy and may prevent progression to a more serious stage.

Bed Rest

Absolute bed rest is important in therapy because physical exercise will aggravate HAPE by increasing pulmonary artery pressure and reducing arterial oxygen saturation. Results of studies in Peru have shown that HAPE can be treated with bed rest alone at high altitude, without oxygen administration or descent.[20] In severe cases, recovery is slower with bed rest than when oxygen is used. Mild cases of HAPE can be treated at high altitudes without descent by one to two days of bed rest. Serial examinations of the chest and measurement of heart rate and respiratory rate, as well as evaluation of symptoms, are necessary; if deterioration occurs, there should be prompt assistance to a lower altitude.

Descent to a Lower Altitude

There are many reports of persons with HAPE whose conditions have improved on descent to a lower altitude. A descent of even 2,000 or 3,000 feet may result in improvement because at high altitude oxygen saturation lies on the steep part of the oxygen-dissociation curve and small changes in altitude and resultant pressure of inspired oxygen (PIO_2) will be accompanied by major changes in arterial oxygen saturation. For climbing parties at high altitude, descent to a lower altitude may be the only method of treatment available. Early recognition of mild symptoms will permit the victim to be helped to a lower altitude before serious HAPE occurs and the victim is unable to walk. If symptoms are severe, evacuation by a litter will be necessary because the effort of climbing down may increase the severity of HAPE.

Oxygen

The administration of 100 percent oxygen is the most effective and rapid method of treating HAPE (Figure 3). Results of studies in Peru have shown that oxygen administration will rapidly

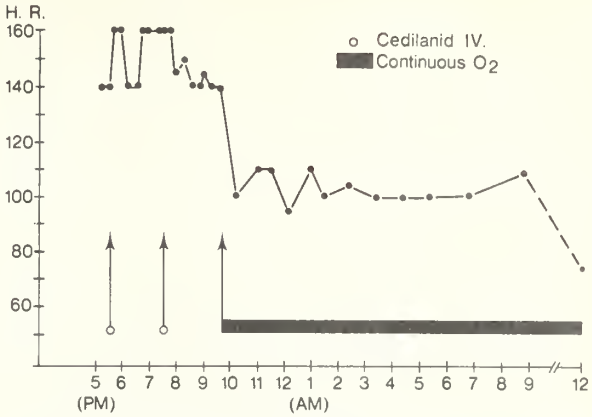

Figure 3.—Effect of digitalis and oxygen upon the heart rate in acute severe high altitude pulmonary edema studied at 12,500 feet. Cedilanid, 0.3 mg given intravenously, was administered in doses two hours apart as shown by the arrows. There were no changes in physical signs and dyspnea became worse. Prompt relief of symptoms and clinical improvement occurred with 100 percent oxygen **(third arrow).** (Reprinted from Hultgren,[38] p 477, by permission of Marcel Dekker, Inc.)

increase arterial oxygen saturation, lower pulmonary artery pressure, reduce heart rate and respiratory rate, and relieve symptoms. In field conditions oxygen can be effectively administered with a plastic face mask.[30] High flow rates of 6 to 8 liters per minute should be used for the first 15 to 30 minutes because of the rapid respiratory rate. To conserve oxygen, rates of 2 to 4 liters per minute can be used for 12 to 48 hours until recovery or evacuation to a lower altitude. Rescue teams or helicopters should carry oxygen to the victim so that therapy can be begun immediately. Treatment by descent and administration of oxygen has been described vividly in a severe case of HAPE occurring during the 1969 American Dhaulagiri expedition.[31] New lightweight portable oxygen tanks are available (see Acute Mountain Sickness section).

Drug Therapy

Evaluating the effect of drug intervention in cases of HAPE is difficult for several reasons: (1) HAPE usually occurs in the mountains, where facilities for systematic studies are not available. (2) Treatment by bed rest, removal to a lower altitude or oxygen administration may be done at the same time; consequently, the effect of drug intervention alone cannot be evaluated. (3) No animal model of HAPE is available that would permit proper investigation of drug intervention. (4) Anecdotal reports of alleged successful use of drugs are common and tend to be repeated in

the literature, whereas failure of drug therapy is rarely reported.

Diuretics such as furosemide have been used in patients with HAPE, and workers in India have recommended furosemide for prevention and treatment of HAPE. There are several physiologic features that suggest that a diuretic would be of limited value in treatment: (1) Blood volume is low due to fluid loss into the lungs, fluid loss by the respiratory tract and inadequate fluid intake. (2) Cardiac output and systemic blood pressure are low. (3) Left ventricular failure is not present. In these circumstances, a further decrease in plasma volume by diuresis may lower blood pressure, cardiac output and perfusion of vital organs. In the mountains this may result in a patient's inability to walk; consequently, there may be difficulty evacuating the patient.[17] Furosemide therapy has been shown to be of no value in preventing acute mountain sickness, and it results in a high incidence of postural hypotension and syncope.[32,33] The degree of body hydration has shown no relation to the incidence of severity of acute mountain sickness.[34] Proponents of diuretic therapy argue that furosemide has a dilating effect in the veins and may also reduce cerebral edema. These effects have not been shown in patients with HAPE. With no clear evidence of benefit and with the potential of harmful side effects, it is prudent not to use diuretics for preventing or treating HAPE until further data are available.

Morphine has also been used in treating HAPE, probably because of its traditional use in cases of cardiac pulmonary edema.[21,22,35] The use of morphine in HAPE has not been subjected to adequately controlled studies and, until beneficial effects have clearly been shown, its use should be avoided. Unfavorable effects have been reported. The depressant effect of morphine on ventilation could increase the severity of hypoxia, an important cause of HAPE.

Other drugs such as digoxin, isoproterenol preparations and steroids have no proven value in the treatment of HAPE.

Prevention

Because the occurrence of HAPE is related to the speed of ascent, the altitude reached and the amount of physical exertion at high altitude, the most effective means of prevention is acclimatization—either by slow ascent or a sojourn of several days at an intermediate altitude. High altitude pulmonary edema is being reported with increasing frequency in places where unacclimatized persons travel rapidly to high altitudes. These places include Colorado ski areas, Kilimanjaro and Mount Kenya in Africa, the Mount Everest base camp in India, and the Argentinian and Peruvian Andes. Houston recommends one day per 500 feet of ascent from 9,000 feet and above, interrupted by a day of partial rest at 14,000 and 18,000 feet.[16] This pace may be too slow. Experienced Himalayan trekkers advise two rest days during an ascent from 11,000 to 15,000 feet.

Heavy physical activity on arrival at high altitude should be avoided during the first two to five days, especially if ascent has been rapid. Mild cases of HAPE may be treated at high altitude by one to two days of bed rest provided that deterioration does not occur.

In well controlled studies,[36] it has been shown that use of acetazolamide reduces the incidence and severity of acute mountain sickness. Side effects are minimal and disappear when administration of the drug is stopped. Results of preliminary studies have suggested that acetazolamide may be of value in preventing recurrent HAPE in susceptible persons, but other workers have noted failure with this medication.[33] Acetazolamide, in a dose of 250 mg, is administered once or twice a day beginning on the day of ascent and continuing for three to five days after arrival at high altitude. Administration of the drug should not be continued for more than seven days. One 250 mg dose of acetazolamide at night may promote more restful sleep.

Furosemide and other diuretic agents have not been shown to be valuable in preventing HAPE.

Physiologic Features

Hemodynamics. Pulmonary hypertension due to an increased pulmonary vascular resistance is consistently found in patients with HAPE. Pulmonary artery wedge and left atrial pressures are normal or low.[13,37] Cardiac output is decreased and systemic blood pressure is low. Right atrial pressure is normal or occasionally raised. Blood pressure response to the Valsalva maneuver is normal.[14]

Hemodynamic studies of persons who have recovered from HAPE have shown normal values and normal responses to exercise. Data from a few patients suggest that a rise in pulmonary

artery pressure during exercise and during acute hypoxia may be greater than that in normal persons.

Blood Gases. Arterial oxygen saturation is decreased with HAPE, often to very low levels. The carbon dioxide pressure is decreased or normal and the pH is increased.[37-39] Exercise or induced hypoxia results in an increase in pulmonary artery pressure and a fall in arterial oxygen saturation.

Administration of 100 percent oxygen is accompanied by a prompt rise in arterial oxygen saturation but normal values are usually not attained; this suggests that there is intrapulmonary shunting. Oxygen administration will rapidly lower pulmonary artery pressure, but normal levels are not usually attained.

Pathologic Conditions

Autopsy findings in fatal cases of HAPE have been reported by several workers.[24,40,41] Severe, confluent pulmonary edema is present, with a protein-rich exudate filling the alveoli. In some cases fibrinous intraalveolar exudates or hyaline membranes are present that are like those seen in influenzal pneumonia in patients with mitral stenosis, or in the respiratory distress syndrome of infants. Such deposits are usually found when very high capillary pressures occur or when capillarly injury is present with increased permeability to protein. Hemorrhage into alveoli may occur. Pronounced capillary congestion and distension of capillaries by erythrocytes is commonly found. Obstruction of capillaries and arterioles by thrombi consisting of platelet aggregates, leukocytes, red cells and fibrin strands or clumps have been described. Numerous megakaryocytes may be present in such aggregates.[24] Notable dilatation of preterminal arterioles, capillaries and small pulmonary veins has also been observed.[40]

Pneumonitis is rare. In one patient with pneumonitis the clinical history suggested that a viral respiratory infection existed before HAPE occurred.[24] Pneumonitis may have facilitated HAPE; pneumonia in experimental animals increases capillary permeability and susceptibility to pulmonary edema.

The right atrium, right ventricle and large pulmonary arteries are usually distended and hepatic congestion may be present. Signs of left ventricle failure are absent. The left ventricle, left atrium and pulmonary veins are not distended. Underlying cardiac or pulmonary disease is absent.

Cerebral edema related to severe hypoxia may occur.[16,17,21]

Causes

The causes of HAPE must be considered within the framework of the following well-established features of this unusual form of pulmonary edema: (1) a rapid rise in pulmonary artery pressure due to high altitude ascent, with a low pulmonary artery wedge and left atrial pressure; (2) acute hypoxic pulmonary arteriolar vasoconstriction, which is reversed on breathing oxygen; (3) absence of left ventricular failure or pneumonia; (4) pronounced pulmonary capillary congestion and presence of capillary and arterial thromboses in many fatal cases; (5) harmful effect of heavy exercise, but improvement with bed rest.

In 1966 the author proposed the following concept of the etiologic factors in HAPE.[38,42] It was proposed that the primary cause of HAPE was nonhomogeneous obstruction of the pulmonary vascular bed by hypoxic vasoconstriction and possibly intravascular thromboses. During periods of exercise and increased pulmonary blood flow, unobstructed areas of the pulmonary circulation would be subjected to high pressure and flow; the precapillary arterioles would become dilated, permitting the high pulmonary artery pressure to be transmitted directly to the capillary bed, with resulting interstitial and alveolar edema. With dilation of arterioles and capillaries, pulmonary veins may then become the site of resistance to flow, which would also result in a high capillary pressure. Therefore, an important mechanism of HAPE is failure of hypoxic vasoconstriction and dilatation of nonconstricted vessels in local areas of the lung. A similar concept has been proposed for the mechanism of hypertensive encephalopathy in systemic hypertension. It is proposed that in this condition cerebral edema is due to failure of cerebral vasoconstriction, permitting a high arterial pressure to be transmitted to the capillary bed with resultant edema. Failure of vasoconstriction seems to occur when a very high arterial pressure is present. The degree of pressure elevation is thought to be the cause. Clinical and experimental evidence supporting this concept is available.[43-45]

Reports of Cases

CASE 1. An example of severe, nonfatal pulmonary edema in a skier is illustrated by the following report. A 41-year-old man skied at Mam-

moth, California, during the Christmas holidays. On both December 23 and 24 he skied at altitudes between 8,500 and 10,000 feet. On the afternoon of the second day he noted unusual fatigue and dyspnea, and felt "feverish." On the third day he felt no better and saw a local physician. An x-ray film of the chest showed "pulmonary infiltrate" and he was given 1.2 million units of penicillin intramuscularly. On the fourth day he still felt ill, a second injection of penicillin was given. He continued to ski and on the sixth day he had extreme difficulty breathing and was weak. He retired to his room and was found soon thereafter in a semicomatose state.

He was taken to a hospital in Bishop, California, (altitude 4,100 feet) by ambulance. On arrival he was able to respond only to his name. Pronounced cyanosis was present. Blood pressure was 105/60 mm of mercury, pulse rate was 160, respirations were 30 per minute and temperature was 38.4°C (101.2°F). Bilateral, moist, bubbling rales were present in both lung fields. No other abnormalities were noted. Hematocrit was 52 percent; leukocyte count was 21,000 per cu mm, with 80 percent polymorphonuclear neutrophils. Arterial blood gas values were oxygen pressure, 32 mm of mercury; carbon dioxide pressure, 32 mm of mercury; pH, 7.46. Serum enzymes were normal. An electrocardiogram showed atrial flutter (2:1 atrioventricular block) and signs of moderate acute right heart strain. Administration of 100 percent oxygen by face mask increased arterial oxygen pressure to 52 mm of mercury. An x-ray film of the chest showed a normal heart. Numerous fluffy infiltrates were present in all lung fields especially in the right mid-lung field where a confluent infiltrate was present. There was no history of cardiac or pulmonary disease, or altitude intolerance.

Treatment with bed rest and administration of 100 percent oxygen and digoxin resulted in rapid improvement. On the second hospital day sinus rhythm returned, aterial oxygen pressure was 99 mm of mercury with the patient breathing 100 percent oxygen, and his mental state was normal. On the third hospital day nearly complete clearing of the infiltrate was noted. The leukocye count was 11,000 per cu mm with 60 percent polymorphonuclear.

On the fifth day recovery was complete and the patient was referred to a medical center in the San Francisco Bay area for further studies. No cardiac or pulmonary abnormalities were noted.

The patient nearly died; previous experience indicates that when mental dysfunction or coma occurs as a result of severe hypoxia, death will occur within a few hours unless descent or oxygen therapy is initiated. An incorrect diagnosis of pneumonitis complicated the situation. Descent to a lower elevation when the pulmonary infiltrate was detected probably would have resulted in complete recovery. Atrial flutter is rare in HAPE, but acute right ventricle strain due to acute pulmonary hypertension is common. Right atrial distention probably contributed to the onset of atrial flutter.

HAPE in skiers is more common in the Rocky Mountains, but a previous episode has been reported from the Mammoth Lake area in California. The altitude of overnight accommodations there is 8,500 feet and skiers can ascend to 10,000 feet. No known cases have been observed in the Lake Tahoe area where most overnight accommodations are at 6,200 feet. HAPE usually occurs when skiers sleep above 7,000 feet.

CASE 2. A 38-year-old healthy man, an experienced mountaineer, was climbing in the Cordillera Blanca in Peru. In three days he climbed with a heavy pack from 9,000 to 14,000 feet over a series of ridges, one of which was 16,000 feet. On the evening of the third day he was more tired than other members of the party and had Cheyne-Stokes respirations. The following day he engaged in light activity only, but on the fifth day he climbed steep slopes with a heavy pack to a higher camp. He was far more short of breath than other members of the party, and upon arrival at the 16,000 foot camp was tired and listless and could not eat. He began to cough and one of his companions said that he "obviously had fluid in his lungs." He was comfortable only in a seated position. Because he was thought to have pneumonia, he was given penicillin. His breathing rapidly became more labored, and his cough became more severe and frequent. His companion, who was not a physician, wrote in his diary "the next few hours his breathing became progressively more congested and labored. He sounded as though he were literally drowning in his own fluid with an almost continuous loud bubbling sound as if breathing through liquid." During the night his breathing became far worse and he lost consciousness. He died at dawn on the second day of illness. His companion stated in his diary "a couple of hours after his death, when we got up to carry on the day's activities,

I noticed that white froth resembling cotton candy had appeared to well up out of his mouth." An autopsy done five days after death disclosed findings compatible with severe pulmonary edema. At the time of this incident high altitude pulmonary edema had not been recognized, so there was no prompt evacuation to a lower altitude—which might have been lifesaving.

An analysis of 33 instances of HAPE occurring in mountain climbers is shown in Table 2.

Cerebral Edema of High Altitude

In 1959 Chiodi described a patient who had predominantly neurological symptoms and signs during exposure to high altitude in the Andes.[46] Occipital headaches were intense and associated with cervical pain. Tinnitus was troublesome. Areas of anesthesia and paresthesia, particularly in the arms and legs, were present. Paralysis of the arms and legs, as well as hemiplegia, occurred. There was severe pain in the limbs, joints and lumbar regions. Examination showed cervical rigidity, ankle clonus, an abnormal Babinski sign, localized areas of cutaneous anesthesia and dilatation of retinal veins. On lumbar puncture, the spinal fluid was bloody but dynamics were normal. Symptoms and signs disappeared promptly on return to sea level. There was no evidence of unusual polycythemia or alveolar hypoventilation. A cerebral arteriogram and cerebral blood flow studies were normal. The usual increase in cerebral blood flow in response to low-oxygen breathing was absent and Chiodi suggests that this may be a factor in the development of the clinical features.

Subsequently, many instances of high altitude illness characterized by cerebral and neurologic symptoms and signs associated with mental dysfunction, confusion, stupor or coma have been observed at high altitudes.[16,17,21] Findings from autopies have shown cerebral edema. Because the syndrome has sometimes occurred without symptoms and signs of HAPE, it is likely that cerebral edema represents another manifestation of high altitude exposure. Data from a small number of cases have shown that papilledema, retinal hemorrhage and increased cerebrospinal fluid pressure are present. In one instance the symptoms were so suggestive of a subdural hematoma or neoplasm that a craniotomy was done. Cerebral edema was noted and a biopsy of the brain appeared to confirm the gross diagnosis.[47] A possible mechanism is the effect of severe hypoxia on the brain with inhibition of the sodium pump and intracellular edema. Cerebral edema has been observed in monkeys subjected to an altitude of 18,000 feet in a low pressure chamber.[48] It has been proved that hypoxia results in cerebral edema in humans.[49] Prompt removal to a low altitude and use of oxygen therapy will result in recovery. Late neurologic complications are rare and mental processes appear to recover completely.

Retinal Hemorrhage

A study carried out at Mount Logan (17,500 feet) in the Yukon Territory in 1968 led to the discovery that retinal hemorrhage may occur above 10,000 feet. In most instances symptoms are absent, but in some persons there is visual

TABLE 2.—*Analysis of 33 Instances of HAPE in Climbers*

	Mean	*Range*
Age	30 years	20 to 43 years
Altitude of occurrence	13,670 feet	8,600 to 24,000 feet
Duration of ascent	3.9 days	1 to 11 days
Interval before onset of symptoms	3 days	1 to 11 days
Most common features	Cough (24) Shortness of breath (20) Fatigue (16) Confusion, mental changes (16) Gurgling in chest (14)	
Pulse rate	115 per minute	96 to 170 per minute
Duration of edema	5.2 days	2 to 10 days
Previous episodes of HAPE	4 (12 percent)	
Deaths	9 (27 percent)	

HAPE = high altitude pulmonary edema

disturbance (clouding of vision). Ophthalmoscopy shows retinal hemorrhage which may be multiple, bilateral and occasionally severe enough to obscure the macula. Pronounced hyperemia near the optic disk, tortuousness and increased diameter of veins and arteries are present. These changes may occur without hemorrhage. Descent to sea level results in recovery in two to six weeks. Permanent visual impairment is rarely observed. The mechanism is not clear. Afflicted persons may have no other symptoms and papilledema is not always present. Studies done at Mount Logan have shown that retinal blood flow increases at high altitude.[50,51] Increased flow and pressure, combined with hypoxic injury to the retinal vascular bed, are probable causes. Intraocular pressures are normal.[52] Retinal hemorrhage has been observed in hypoxic states in persons at sea level. Carbon monoxide poisoning is frequently accompanied by retinal hemorrhage.

Systemic Edema at High Altitudes

Asymptomatic edema of the face, hands and feet, associated with a weight gain of 4 to 12 pounds for four to ten days at high altitudes, is most common in women. Puffiness of the face and eyelids in the morning after sleep may be troublesome and unsightly. Edema may occur in the absence of other symptoms of altitude illness. In susceptible persons repeated episodes during each exposure to altitude are common. Upon return to sea level, diuresis with weight loss occurs. Edema may persist for one to three days after return to a lower altitude. The cause is not clear. There appears to be no relation to the menstrual cycle or the use of birth control pills. It is possible that sodium and water retention is stimulated by the decrease in plasma volume that occurs during high altitude exposure.[53-55] Published data regarding this syndrome are minimal and studies of etiologic mechanisms are clearly indicated.[56,57]

Prevention and treatment by the use of furosemide or other diuretic agents is usually effective. Salt intake should be reduced.

The following case report illustrates the problem of systemic edema at high altitude associated with AMS. Relief was obtained by the use of acetazolamide and furosemide.

CASE 3. A 48-year-old housewife has had "altitude sickness" for several years during annual two-week backpacking trips to the Sierra Nevadas at altitudes between 8,000 and 10,000 feet. She was healthy and there was no history of cardiopulmonary or renal disease, or unusual edema during pregnancies. Her mother and maternal grandmother both had had periodic edema of the ankle. Within 24 hours of arrival at high altitudes, headache, nausea, anorexia and fatigue appear and continue for four to six days. On the third to fourth day, edema of the face and eyelids usually appears followed by edema of the feet, ankles and lower legs ("Legs feel heavy").

No abnormalities were found on physical examination, electrocardiogram, x-ray studies of the chest or routine laboratory studies. Serum albumin values were normal.

The patient was advised to use acetazolamide, 250 mg once a day, on the day of ascent and for three days after arrival. Acetylsalicylic acid and a compound of acetylsalicylic acid, phenacetin and caffeine (Empirin Compound) were prescribed for headache. Furosemide, 40 mg, was suggested for use if edema appeared.

The following summer the patient reported the results of a two-week return trip to the High Sierras. The patient was in a premenstrual period and menstrual flow began eight days after arrival at high altitude. She took 250 mg of acetazolamide on the day of ascent and once a day for four days after arrival. A minor headache was noted on the fourth and fifth days, as well as slight numbness and tingling of the finger tips. On the sixth and seventh days moderate edema of the face, eyelids and lower legs appeared. Furosemide, 40 mg, was taken once a day for two days and resulted in diuresis and complete relief of edema. Five days later edema returned; the patient descended to sea level and spontaneous diuresis occurred with loss of edema. The patient said that this was her "first fully enjoyable trip to the mountains in many years." Numbness and tingling of the fingers are common side effects of acetazolamide therapy. The second episode of edema should have been treated with furosemide.

Thrombotic Disease of High Altitude

Exposure to very high altitudes may be accompanied by pulmonary embolism or cerebral thrombosis. During the first attempt by Houston's group to climb K2 in Kashmir, pulmonary embolism developed in one of the climbers and he died during descent. At 22,000 feet on Makalu, Hillary sustained a transient stroke and had to descend. Other episodes have been described by Ward.[58] Such complications are rare but are most

likely to occur at very high altitudes, especially in bad weather when prolonged stay in a tent with no activity and inadequate fluid intake are common.

Thrombotic obstruction of the pulmonary vascular bed may play a role in causing HAPE. Studies of changes in clotting factors in persons ascending to high altitudes have indicated that there may be evidence of increased coagulability or thrombosis.[59-61]

Effect of High Altitudes on Sea Level Medical Problems

Several medical conditions clearly are adversely affected by high altitudes: (1) primary pulmonary hypertension, (2) cyanotic congenital heart disease, (3) chronic pulmonary disease with arterial unsaturation, (4) coronary artery disease with severe angina or cardiac failure, (5) congestive failure with arterial unsaturation.

Patients with primary pulmonary hypertension who have decreased arterial oxygen saturation, or in whom there is a rise in pulmonary vascular resistance with hypoxia, should not be exposed to even moderate altitudes. Symptoms of patients living at high altitudes will usually improve when they move to sea level.[62]

In patients with even modest degrees of arterial unsaturation, pronounced decreases in oxygen saturation may occur with exposure to only moderate altitudes. This is due to the fact that they are on the steep part of the oxygen dissociation curve where a modest change in inspired Po_2 will cause greater changes in arterial saturation than occurs in normal persons.

In patients with coronary disease or cardiac failure, hypoxia will not only decrease oxygen supply to the myocardium but will increase cardiac work by an increase in heart rate and an increase in the work of breathing.

When patients with one of the conditions mentioned above must travel to high altitudes for a short time, or must travel long distances by air, oxygen should be provided to relieve symptoms if necessary. If the disease is mild, patients may be permitted to travel to high altitudes for a short time. They should be cautioned to avoid physical activity for the first two to three days, to use oxygen if necessary and to descend if symptoms persist. High altitudes can be tolerated by many patients after an initial rest of a few days.

Patients with chronic obstructive pulmonary disease who do not have notable arterial unsaturation may ascend to moderate altitudes without serious symptoms or deterioration in pulmonary function. If arterial unsaturation is present at sea level, it will increase at high altitude. Houston studied eight cases of mild to moderate chronic obstructive disease at sea level and at 6,340 feet. Arterial Pao_2 at sea level was 66 mm of mercury. This dropped to 52 mm at high altitude, and during exercise a Pao_2 of 47 mm was noted.[63] It is possible that some patients with obstructive airway disease may do better at high altitude because of the reduced air density.

Airline travel may have the same effect as acute high altitude exposure with equivalent altitudes of between 1,000 and 8,000 feet. Cabin altitudes rarely exceed an equivalent elevation of 8,000 feet, but at this altitude the arterial Po_2 is 55 mm of mercury. A patient with pulmonary disease should not undertake long airline flights unless the arterial Po_2 and Pco_2 are at reasonable levels at sea level. In doubtful cases, oxygen must be available during the journey. Recommendations to airlines and patients should be specific. High concentrations of oxygen should not be used because of the danger of carbon dioxide retention. A Venturi mask which delivers from 25 percent to 30 percent oxygen is recommended.[64]

Patients with pneumothorax should not fly or ascend to high altitudes. Hazards of high altitudes were more common in earlier years when therapeutic pneumothorax or pneumoperitoneum was used in treating tuberculosis, and cabin altitudes in aircraft were higher.

Chronic high altitude exposure does not have an adverse effect in persons with essential hypertension. Several studies have shown that systolic blood pressure is lower in normal residents at high altitude than in a similar population at sea level.[1,62,65] Systolic pressure is decreased more than diastolic pressure. Cardiac output is normal.[1] Results of studies in persons who have moved from sea level to the Peruvian Andes have shown that after five to ten years of living at high altitudes the expected rise in blood pressure with increasing age does not occur. Instead there is a major fall in systolic pressure and a lesser decrease in diastolic pressure.[66,67] Results of one study have shown no adverse effect of high altitude exposure in patients with essential hypertension.

In patients with sickle cell disease or sickle cell trait an increase in sickling or splenic infarction may develop at high altitude. Although elevations

of 15,000 feet must be attained to reduce the capillary oxygen tension to a level where sickling will occur (Po_2, 10 to 15 mm) episodes of sickle cell crises have been observed in Peru at elevations between 3,500 and 4,500 meters (11,483 and 14,764 feet).[68]

Despite the large number of patients with mild or moderate chronic disease, as well as the elderly persons who travel to high altitude regions, our knowledge of the effect of high altitudes in such situations is woefully inadequate. Further research in this area is clearly needed.

Drug Effects at High Altitudes

Another area in which our knowledge is deficient is the effect of high altitudes in persons using common medications. Barbiturates, for example, may have a greater soporific effect at high altitudes than at sea level and should be used with caution. The depressant effect of such drugs on respiration during sleep may accentuate hypoxia and result in increasing the severity of AMS.

It is well known that a person's tolerance to alcohol is diminished at high altitude. Part of this effect may be due to diminished clearance by the liver.

Problems of anesthesia at high altitude have been reviewed by Safar and Tenicela.[69] Prolonged effects from hypnotic agents, opiates and barbiturates may occur and may be partly corrected by the use of oxygen. Many hospitals and medical facilities are located at high altitudes, such as at La Paz, Bolivia (12,000 feet) and Cerro de Pasco, Peru (14,200 feet).

Patients who are receiving oral anticoagulant agents should check their prothrombin levels frequently at high altitude because hepatic hypoxia may result in a more profound decrease in prothrombin levels.[70]

Furosemide has been recommended for the prevention and treatment of AMS and HAPE. The drug does not reduce symptoms of AMS.[71] It has been noted that the use of furosemide by normal persons, even in small doses (40 mg once or twice a day), results in a substantial incidence of postural hypotension and near syncope.[17,32,33] This effect is more severe at high altitudes than at sea level because of the decrease in plasma volume that normally occurs on ascent to high altitudes. This decrease may be as much as 20 percent to 30 percent.[54,55]

Medical and physiologic problems associated with high altitudes will continue to be a rewarding area of research. Our knowledge of most altitude problems is still in the stage of infancy. For readers interested in other sources several references can be highly recommended. In *Barometric Pressure* by Bert, some of the earliest experiments relating to hypoxia and altitude exposure are recorded.[72] In *Life of Man on the High Alps* by Mosso, the earliest experiments done in the mountains of Europe are recorded.[73] Barcroft's *Lessons from High Altitude* describes the first scientific studies done on the effects of high altitudes on persons in the Andes.[6] *Mountain Medicine* by Ward and *Man at High Altitude* by Heath and Williams are recent publications that summarize much of our current knowledge about high altitude exposure.[58,74]

REFERENCES

1. Banchero N, Sime F, Peñaloza D, et al: Pulmonary pressure, cardiac output, and arterial oxygen saturation during exercise at high altitude and at sea level. Circulation 33:249-262, Feb 1966
2. West H, Lahiri S, Gill M, et al: Arterial oxygen saturation during exercise at high altitude. J Appl Physiol 17:617-621, Jul 1962
3. Vogel J, Weaver W, Rose R, et al: Pulmonary hypertension on exertion in normal man living at 10,150 ft. (Leadville, Colorado). Med Thorac 19:461-477, 1962
4. Powles A, Sutton J, Gray G, et al: Ventilatory responsiveness at sea level and sleep hypoxemia at altitude (abstract). Clin Res 25:672A, Dec 1977
5. Jarcho S: Mountain sickness as described by Fray Joseph De Acosta, 1589. Am J Cardiol 2:246-247, 1958
6. Barcroft J: Respiratory functions of the blood. *In* Lessons from High Altitudes, Vol 1. London, Cambridge University Press, 1925
7. Hackett P, Rennie D: The incidence, importance and prophylaxis of acute mountain sickness. Lancet 2:1149-1154, Nov 27, 1976
8. Evans WO, Robinson SM, Horstman DH, et al: Amelioration of the symptoms of acute mountain sickness by staging and acetazolamide. Aviat Space Environ Med 47:512-516, May 1976
9. Carson RP, Evans WO, Shields JL, et al: Symptomatology, pathophysiology and treatment of acute mountain sickness. Fed Proc 28:1085-1091, May-Jun 1969
10. Falchuk K, Lamb T, Tenney S: Ventilatory response to hypoxia and CO_2 following CO_2 exposure and $NaHCO_3$ ingestion. J Appl Physiol 21:393-398, Mar 1966
11. Peñaloza D, Sime F: Chronic cor pulmonale due to loss of altitude acclimatization (chronic mountain sickness). Am J Med 50:728-743, Jun 1971
12. Arias-Stella J, Krüger H, Recavarren S: Pathology of chronic mountain sickness. Thorax 28:701-708, Nov 1973
13. Kryger M, Glas R, Jackson D, et al: Impaired oxygenation during sleep in excessive polycythemia of high altitude: Improvement with respiratory stimulation. Sleep 1:3-17, Sep 1978
14. Hultgren H, Lopez C, Lundberg E, et al: Physiologic studies of pulmonary edema at high altitude. Circulation 29:393-408, Mar 1964
15. Grover R, Vogel J, Voigt C, et al: Reversal of high altitude pulmonary hypertension. Am J Cardiol 18:928-932, Dec 1966
16. Houston C, Dickinson J: Cerebral form of high altitude illness. Lancet 2:758-761, Oct 18, 1975
17. Wilson R: Acute high altitude illness in mountaineers and problems of rescue. Ann Intern Med 78:421-428, Mar 1973
18. Hultgren H, Spickard W, Hellriegel K, et al: High altitude pulmonary edema. Medicine 40:289-313, Sep 1961
19. Hultgren H: High altitude pulmonary edema, *In* Vogel JK (Ed): Hypoxia, High Altitude and the Heart—First Conference on Cardiovascular Disease, Vol. 5, Aspen, Colo. 1970. Basel, Munich, Paris, New York, Karger, 1970, pp 24-31
20. Marticorena E, Hultgren H: Evaluation of therapeutic methods in high altitude pulmonary edema. Am J Cardiol (In press)
21. Singh I, Kapila C, Khanna PK, et al: High altitude pulmonary edema. Lancet 1:229-234, Jan 30, 1965
22. Menon N: High altitude pulmonary edema. N Engl J Med 273:66-73, Jul 1965
23. Hultgren H, Marticorena E: High altitude pulmonary edema: Epidemiologic observations in Peru. Chest 74:372-376, Oct 1978
24. Hultgren H, Spickard W, Lopez C: Further studies of high altitude pulmonary edema. Br Heart J 24:95-102, Jan 1962

25. Peñaloza D, Arias-Stella J, Sime F, et al: The heart and pulmonary circulation in children at high altitudes. Pediatrics 34: 568-582, Oct 1964

26. Scoggin C, Hyers T, Reeves J, et al: High altitude pulmonary edema in children and young adults of Leadville, Colorado. N Engl J Med 297:1269-1272, Dec 8, 1977

27. Hultgren H, Grover R, Hartley L: Abnormal circulatory responses to high altitude in subjects with a previous history of high altitude pulmonary edema. Circulation 44:759-770, Nov 1971

28. Peñaloza D, Sime F: Circulatory dynamics during high altitude pulmonary edema. Am J Cardiol 23:369-378, Mar 1969

29. Kleiner J, Nelson W: High altitude pulmonary edema—A rare disease? JAMA 234:491-495, Nov 3, 1975

30. Hultgren H: Treatment and prevention of high altitude pulmonary edema. American Alpine J 14:363-372, 1965

31. Read W, Morrissey J, Reichardt L: American Dhaulagiri Expedition 1969. American Alpine J 17:19-26, 1970

32. Hultgren H, Bilisoly J, Fails H, et al: Plasma volume changes during acute exposure to high altitude (abstract). Clin Res 21:224, Feb 1973

33. Gray GW, Bryan AC, Frayser R, et al: Control of acute mountain sickness. Aerosp Med 48:81-84, Jan 1971

34. Aoki V, Robinson S: Body hydration and the incidence and severity of acute mountain sickness. J Appl Physiol 31:363-366, Sep 1971

35. Singh I, Khanna PK, Srivastava M, et al: Acute mountain sickness. N Engl J Med 280:175-184, Jan 1969

36. Forwand SA, Landowne M, Follansbee JN et al: Effect of acetazolamide on acute mountain sickness. N Engl J Med 279: 839-845, Oct 1968

37. Fred H, Schmidt A, Bates T, Hecht H: Acute pulmonary edema of altitude—Clinical and physiologic observations. Circulation 25:929-937, Jan 1962

38. Hultgren HN: High altitude pulmonary edema, *In* Staub N (Ed): Lung Water and Solute Exchange. New York, Marcel Dekker 1978, pp 437-469

39. Grover RF, Hultgren HN, Hartley LH: Pathogenesis of acute pulmonary edema at high altitude, *In* Giuntini C (Ed): Central Hemodynamics and Gas Exchange. Torino, Minerva Medica, 1971, pp 409-420

40. Arias-Stella J, Kruger H: Pathology of high altitude pulmonary edema. Arch Pathol 76:147-157, Aug 1963

41. Nayak N, Roy S, Narayanan TK: Pathologic features of altitude sickness. Am J Pathol 45:381-391, Sep 1964

42. Hultgren H, Robinson M, Wuerflein R: Overperfusion pulmonary edema (abstract). Circulation 34(Suppl III):132, Oct 1966

43. Lassen N: Control of cerebral circulation in health and disease. Circ Res 34:749-760, Jun 1974

44. Johansson B, Strandgaard S, Lassen N: On the pathogenesis of hypertensive encephalopathy: The hypertensive "breakthrough" of autoregulation of cerebral blood flow with forced vasodilatation, flow increase, and blood-brain-barrier damage. Circ Res 34&35(Suppy I):I-167-I-171, May 1974

45. Skinhoj E, Strandgaard S: Pathogenesis of hypertensive encephalopathy. Lancet 1:461-462, Mar 3, 1973

46. Chiodi H: Mal de montana a forma cerebral: Posible mechanismo etiopatogenico. An Fac Med Lima 43:437, 2nd trimestre, 1960

47. Roy S, Singh I: Acute mountain sickness in Himalayan terrain: Clinical and physiological studies, *In* Hegnauer A (Ed): Biomedical Problems of High Terresterial Elevations. Natick, Mass, U.S. Army Research Institute of Environmental Medicine, 1969

48. Kennedy GA, Bucci T, Myers R, et al: Effects of altitude on the Cebus monkey with emphasis on the central nervous system (abstract). Fed Proc 29:591, Mar-Apr 1970

49. White JC, Verlot M, Selverstone B, et al: Changes in brain volume during anesthesia: Effects of anoxia and hypercapnia. Arch Surg 44:1-21, Jan 1942

50. Frayser R, Houston C, Bryan A, et al: Retinal hemorrhage at high altitude. N Engl J Med 282:1183-1184, May 1970

51. Frayser R, Gray GW, Houston CS: Control of the retinal circulation at altitude. J Appl Physiol 37:302-304, Sep 1974

52. Clarke C, Duff J: Mountain sickness, retinal haemorrhages and acclimatization on Mount Everest in 1975. Br Med J 2:495-497, Aug 28, 1976

53. Weiner MW, Weinman E, Kashgarian M, et al: Accelerated reabsorption of the proximal tubule produced by volume depletion. J Clin Invest 50:1379-1385, Jul 1971

54. Hannon JP, Chinn KS, Shields JL: Effects of acute high-altitude exposure on body fluids. Fed Proc 28:1178-1184, May-Jun 1969

55. Surks M, Chinn K, Matoush L: Alterations in body composition in man after acute exposure to high altitude. J Appl Physiol 21:1741-1746, Nov 1966

56. Sumiyoshi K, Sumiyoshi M, Otani N, et al: Changes of blood elements and the circulatory system in climbing. Jap Circ J 26:533-547, Jun 1962

57. Hackett P, Rennie D: Acute mountain sickness (Letter). Lancet 1:1491-1492, Feb 26, 1977

58. Ward M: *In* Mountain Medicine. Crosby, Lockwood, Staples. London, 1975, ch 22, pp 289-292

59. Singh 1, Chohan I, Mathew N: Fibrinolytic activity in high altitude pulmonary oedema. Indian J Med Res 57:210-217, Feb 1969

60. Singh I, Chohan I: Blood coagulation changes at high altitude predisposing to pulmonary hypertension. Br Med J 34: 611-617, Jun 1972

61. Gray GW, Bryan A, Freedman M, et al: Effect of altitude exposure on platelets. J Appl Physiol 39:648-651, Oct 1975

62. Khoury GH, Hawes CR: Primary pulmonary hypertension in children living at high altitude. J Pediatr 62:177-185, Feb 1963

63. Graham WG, Houston CS: Short-term adaptation to moderate altitude—Patients with chronic obsructive pulmonary disease. JAMA 240:1491-1494, Sep 29, 1978

64. Liebman J, Lucas R, Moss A, et al: Airline travel for children with chronic pulmonary disease. Pediatrics 7:408-410, Mar 1976

65. Marticorena E, Severino J, Chavez A: Presión arterial sistemica en el nativo de altura. Arch Inst Biol Andina 2:18, 1967

66. Marticorena E, Ruiz L, Severino J, et al: Systemic blood pressure in white men born at sea level: Changes after long residence at high altitudes. Am J Cardiol 23:365-368, Mar 1969

67. Hultgren H: Reduction of systemic arterial blood pressure at high altitude, *In* Vogel J (Ed): Hypoxia, High Altitude and the Heart. Basel, S. Karger, 1970, pp 49-55

68. Aste-Salazar H, Hurtado A: The affinity of hemoglobin for oxygen at sea level and at high altitude. Am J Physiol 142:733-743, Dec 1944

69. Safar P, Tenicela R: High altitude physiology in relation to anesthesia and inhalation therapy. Anesthesiology 25:515-531, Jul-Aug 1964.

70. Henriksson P, Värendh G, Lundström N-R: Haemostatic defects in cyanotic congenital heart disease. Br Heart J 41:23-27, Jan 1979

71. Aoki VS, Robinson SM: Body hydration and the incidence and severity of acute mountain sickness. J Appl Physiol 31:363-367, Sep 1971

72. Bert P: Barometric Pressure; Researches in Experimental Physiology, translated from the French by M. A. Hitchcock and F. A. Hitchcock. Columbus, Ohio, College Book Co, 1943

73. Mosso A: Life of Man on the High Alps, translated from the second Italian edition by E. Lough Kiesow. London, T. Fisher Unwin, 1908

74. Heath D, Williams D: Man at High Altitude. Edinburgh, Churchill Livingstone, 1977

Specialty Conference

Moderator
EUGENE D. ROBIN, MD

Participants
JOSEPH CUMMISKEY, MD
EUGENE D. ROBIN, MD
JAMES THEODORE, MD
GEORGE CAUGHEY, BS
MICHAEL GORIS, MD
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From Pulmonary Rounds at Stanford University School of Medicine. This has been edited by Doctors Joseph Cummiskey, Andrew Newman, Norman Lewiston and Eugene D. Robin.

Refer to: Cummiskey J, Robin ED, Goris M, et al: Pulmonary arteriovenous communications in the lung—Stanford University School of Medicine Pulmonary Rounds (Specialty Conference). West J Med 131:24-35, Jul 1979

Pulmonary Arteriovenous Communications in the Lung

JOSEPH CUMMISKEY, MD:* This morning we plan to discuss the management of two patients with Rendu-Osler-Weber syndrome, and also to discuss the use of nuclear isotope scanning in this disease and in estimating pulmonary vascular shunts. A 33-year-old woman, a divorced mother of two, came to the Palo Alto Medical Clinic. When she was 22 years old, left hemiplegia and aphasia developed suddenly, and cleared in three to four days. She was taking birth control pills at that time and this was discontinued. Findings on carotid arteriography were inconclusive. Twelve months later, hemoptysis, blood in the feces, dyspnea, poor vision and dizziness developed. No cause was found, but these manifestations cleared spontaneously. She resumed using birth control pills.

EUGENE D. ROBIN:† A condition that appeared to be thrombotic disease involving the central nervous system developed in this patient and subsequently arteriovenous communications were demonstrated. How should the differential diagnosis be approached? Is it clear that the original episode was cerebral thrombosis related presumably to the use of birth control pills? The cerebral vascular disease in this patient could be related to many disorders which produce focal abnormalities of the central nervous system. A diffuse approach to differential diagnosis becomes almost unmanageable because anything is possible.

To be orderly in one's thinking and given two events that can be connected by a single diagnosis, one should favor the single diagnosis rather than assuming that the two events are unconnected. A philosophical approach which is useful in differential diagnosis is known as Ockham's razor. William of Ockham, a 14th century British philosopher, was a nominalist, that is, a believer in the theory that there are no universal essences in reality. Ockham's razor states that the fewer hypotheses required to explain several phenomena, the more likely it is that a correct one will be selected. That is how the word *razor* comes in—one

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shaves the number of hypotheses. The application of Ockham's razor to medicine dictates that a differential diagnosis should be as tight and economical as possible. The physicians caring for this patient used Ockham's razor as follows: The use of birth control pills leads to local thromboses, causing cerebrovascular disease. This is logical because there is substantial evidence that the use of the pill does lead to localized vascular disease, including vascular disease of the brain. Can an alternative hypothesis be given involving arteriovenous (A-V) fistulae?

GEORGE CAUGHEY:* There may have been a brain hemorrhage because of an A-V malformation in the brain.

DR. ROBIN: The thesis would be that A-V malformations lead to cerebral hemorrhage. These vascular malformations are known to be quite thin walled and often bleed (hence the term hemorrhagic). Cerebral hemorrhage is unlikely; the effects of intracerebral hemorrhage tend to be devastating even when bleeding in minor. She recovered completely in three days. Since this is a pulmonary conference can you think of a hypothesis by which pulmonary A-V fistulae could give rise to cerebrovascular lesions?

GEORGE CAUGHEY: There might have been an embolic event because any thrombus or embolism arising in the right side of the heart could pass through the lung.

DR. ROBIN: Good. With A-V fistulae in the lung, the filter function of the pulmonary capillaries which are about 8 micra in diameter is lost. One possibility is that there were A-V fistulae in the patient's lungs that permitted an embolus arising on the right side to traverse sequentially pulmonary veins, left atrium and the systemic circulation to the brain—so-called paradoxical emboli. This discussion may not be as tangential as it sounds because Dr. Goris is going to tell us that he uses paradoxical *emboli* to detect and quantitate the degree of right-to-left shunting in such patients.

DR. CUMMISKEY: Is there not another cause for a cerebral vascular accident (CVA) in this type of case, thrombus formation from increased blood viscosity secondary to the polycythemia of chronic hypoxia?

DR. ROBIN: Is that an acceptable application of Ockham's razor? This requires several extra hypotheses. You add both hypoxemia and erythrocytosis. Both are possible; however, not all pulmonary A-V fistulae give rise to substantial hypoxia and secondary polycythemia.

MICHAEL GORIS, MD:† There is another consideration which is purely statistical. Here is somebody who at age 24 has had three CVA's, which could be emboli. Without A-V fistulae to transmit pulmonary emboli, many of these might have been asymptomatic. However, with pulmonary A-V fistulae, some of these became clinically apparent as brain emboli.

DR. ROBIN: Your point is a good one, and raises a basic issue. I believe that normal people have pulmonary emboli frequently. Trapping emboli is one of the important functions of the lung. Small pulmonary capillaries trap particulates entering the venous circulation. These pulmonary emboli may account for the 5 percent incidence of perfusion defects in perfectly normal people.[1] I can visualize in our patient, then, small showers of paradoxical emboli, one of which happened to involve a critical area of the brain and became clinically manifest. When everything is known about pulmonary emboli, I believe one of the concepts that will emerge is that pulmonary embolism in a sense is a normal process. Most emboli are relatively small, and do not produce the clinical disorder that we call pulmonary embolism.

DR. CUMMISKEY: The patient began to take birth control pills again and again a left hemiplegia developed. She stopped taking the pills and hemiplegia cleared in a week, and again it was assumed that the vascular disease was related to birth control pills. At that time, she was admitted to the Jewish Hospital in Brooklyn. Hematocrit was 55 percent and hemoglobin was 18 grams per dl. The electrocardiogram was normal. An x-ray study of the chest showed multiple circular lesions in the right lower lobe and left lower lobe and one lesion in the right upper lobe which appeared vascular on tomography. Cardiac catheterization showed normal right heart pressures; cardiac output, 6.7 liters per minute; cardiac index, 3.6. Arteriovenous oxygen difference was 4.1 volume percent; arterial oxygen pressure (Po_2), 59 torr; pH, 7.48; arterial carbon dioxide pressure ($Paco_2$), 30 torr on room air. On pulmonary angiography

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multiple pulmonary A-V fistulae were shown in the left lower lobe and the right middle lobe. In the right lower lobe there were three A-V fistulae and one fistula in the right upper lobe. Resection was carried out at that time, with removal of the left lower lobe fistula. Then the left lingular fistula was removed with a subsegmental resection.

JAMES THEODORE, MD:* Do you think that is a curative procedure when dealing with large A-V fistulae? Do you think that once they have removed some of the fistulae, there will be no more problems?

DR. CUMMISKEY: That is a loaded question. If you knew she had Rendu-Osler-Weber syndrome, the answer would be no.

DR. THEODORE: Let's just stay with A-V fistula.

DR. CUMMISKEY: If it was congenital A-V fistula and you removed all of the fistulae, it might be a curative procedure.

DR. THEODORE: That is hard to say. There are a number of circumstances in which they are multiple. When larger fistulae predominate there is always the possibility that the small ones which were relatively inapparent may become more apparent with time. Although surgical operation is the procedure of choice under such circumstances, there is always the possibility that there will be recurrence.

DR. CUMMISKEY: But looking through the literature on A-V malformation, I have seen more than six reports showing that removal of the A-V malformation is curative.[2]

DR. THEODORE: I am not saying patients are not cured of symptoms at that time. The point I am trying to make is that there is always a possibility that another one may develop later. I cannot give you the actual percentages.

DR. ROBIN: Recur?

DR. THEODORE: They have probably been there all along.

DR. ROBIN: The Rendu-Osler-Weber lesions represent, as far as I know, a congenital malformation. My impression of the disease is—and if I am wrong tell me—that persons with the Rendu-Osler-Weber syndrome are born with a preformed package of A-V communications.

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PATRICIA LYNNE-DAVIES, MD:† Are they fully functional though? If in a patient there were two or three which were contributing to a major extent to hypoxemia and which were resected, is it possible that for the next few years some of the remaining communications by redirection of flow might have a more profound effect?

DR. ROBIN: That is an intriguing idea. It appears reasonable to consider that the regulation of flow through A-V fistulae is a dynamic process. Therefore, long-term alterations of pressure-flow relations might alter the contribution of shunts to hypoxemia and might create the impression of formation of new communications.

DR. THEODORE: I did not mean to imply that new ones were forming either in this circumstance or when there are isolated pulmonary AV fistulae.

DR. ROBIN: Let me say that I think that surgical operation, when possible, is by far the best approach for patients who have pulmonary A-V fistulae.

DR. CUMMISKEY: Well, that obviously was the thought in this case, as well. Now the question comes up as to how often reoperation should be considered? There was moderate relief of symptoms with surgical therapy, and there was no further hemoptysis in this patient after the procedure until the age of 28. Then a left CVA developed. This time she was not taking birth control pills, which would argue against your feeling, Dr. Robin, that the birth control pills were contributing to the development of thrombosis.

DR. ROBIN: That was not my conclusion. I suggested that given several possibilities for disease in the brain, I would have picked either A-V communication with hemorrhage or an A-V fistula in the lung with paradoxical emboli. Then Dr. Goris asked if it was possible that there were numerous pulmonary emboli. I answered that this was possible and that birth control pills might have accelerated that process.

S. J. SALFEN, MD:‡ Is it not a fact that the Rendu-Osler-Weber syndrome often presents as a cerebral vascular accident, not for any of those reasons but rather because of a brain abscess from the presumed pre-existing A-V malformation?

DR. ROBIN: The literature I have seen does not

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emphasize the complication of brain abscess as it does in patients with right to left congenital heart disease. I, therefore, thought that the reason there may be infection as a presenting sign, is that the filter function of the lungs is lost, and bacteria in the bloodstream find access to the brain.

ALLAN HANCE, MD:* It must be an infected thrombus.

DR. THEODORE: Without even getting into the specifics of the disease, endarteritis or some kind of infection is always a possibility with any kind of vascular abnormality. I am surprised that with these patients it does not occur more often.

DR. ROBIN: The clinical pearl that I am aware of is that patients with tetralogy of Fallot and with pseudotruncus arteriosus not uncommonly present with brain abscess. This manifestation may be the first clue that congenital cyanotic heart disease is present. I am unaware that the same frequency has been noted in patients with pulmonary A-V fistulae. If this is true, then I think one of the mechanisms might involve the entry of bacteria into the left side of the circulation.

DR. CUMMISKEY: The patient maintains that in 1972, after the third episode of CVA, she diagnosed hereditary hemorrhagic telangiectasia in herself and her family. Karen Hamilton, a medical student, provided a family tree. The mother of our patient had severe epistaxis; her maternal grandmother had hemorrhagic telangiectasia, and now her two children—a daughter aged 7 and a son aged 10—have telangiectasia on their skin and mucous membranes, but are asymptomatic. The patient was next seen, in Ohio, in 1972 because of increasing dyspnea and cyanosis. The hemoglobin value was 16.4 grams per dl. An electrocardiogram was normal. Liver and brain scans were normal. Lung scan was normal. Cardiac catheterization and pulmonary angiograms showed numerous A-V fistulae in the left lower lobe, posterior segment, and the right, middle and right upper lobe, anterior and posterior segments. It was decided not to operate because of the multiple fistulae and because there was uncertainty about which to deal with. Bronchoscopy was done in 1975. The indications are not clear, but the findings were negative.

DR. ROBIN: One reason might be the possibility (with recurrent hemoptysis) of telangiectasia in the bronchial mucosa which are surgically treatable. Surgical therapy may control hemoptysis.

DR. CUMMISKEY: That brings us to the present, when the patient went to the Palo Alto Clinic. One week after the patient was first seen, low right anterior and posterior chest pain developed. Blood pressure was 90/60 mm of mercury; pulse, 65 and regular; respirations, 60; temperature, 36°C (96.8°F). Telangiectasia of the mouth, lips, face and anterior chest; moderate clubbing, and slight cyanosis were noted. Examination of the chest found decreased excursion on the right, dullness in the right base with no friction rub. The S-2 was widely split and the P-2 was greater than A-2. An x-ray film of the chest showed right pleural effusion. Laboratory studies gave the following values: leukocyte count, 12,000 with 12 percent bands; hematocrit, 49 percent; hemoglobin, 16.7 grams per dl. Pa_{O_2} was 60 torr on 35 percent oxygen, pH was 7.47, Pa_{CO_2} was 32 and bicarbonate was 23.

The patient was acutely ill. She was admitted with a diagnosis of possible hemothorax, versus pulmonary embolism. Thoracentesis showed bloody pleural fluid. A pneumothorax developed and a chest tube was placed. When the pneumothorax had resolved, pulmonary function tests were done. The results were interpreted as showing mild restrictive disease; possibly surgical resection could give rise to these changes.

DR. LYNNE-DAVIES: We could say it is mild restrictive disease consistent with a history of surgical resection, but I think it is an excellent example of what you find if you resect what in mechanical terms is normal lung tissue, because all lung volumes are reduced in the same proportion with the result that the residual volume and the expiratory reserve volume are maintained within normal limits.

DR. THEODORE: It might be better to use the terms restrictive defect under the circumstances.

ANTONIUS VAN KESSEL, BS:† What about the effect of pleural disease on the lung volumes? They are so different from normal values—the vital capacity and the total volume are about half normal.

DR. LYNNE-DAVIES: I do not know whether the

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hemoglobin was still elevated or not. I suspect it was at least on the high side of normal.

DR. CUMMISKEY: At that time the hematocrit was elevated. At present the hematocrit is normal (41 percent).

DR. LYNNE-DAVIES: The diffusion capacity is now measured at 100 percent in spite of a degree of restriction which is about 30 percent. I assume that, other things being equal, this means otherwise it would have come out higher than 125 percent—which is acceptable, particularly in the light of the minor degree of polycythemia.

DR. ROBIN: The discussion concerns the fact that among other things the measured diffusing capacity (DLCO) is proportionate to the amount of hemoglobin available to take up carbon monoxide. Many laboratories correct diffusing capacity to a normalized hemoglobin so that the DLCO provides an estimate of diffusing capacity related purely to lung function.

DR. CUMMISKEY: When we first saw the patient (February 1978), blood gas determinations and other studies were carried out with the patient breathing room air under four conditions—supine, standing, exercise and sitting (Table 1). The Pa_{O_2} supine decreased from 61 to 50 torr after the patient had stood for ten minutes. This was a definite drop in the Pa_{O_2} which we felt was due to shunting of more blood through the bases than through the upper lobes of the lung.

DR. ROBIN: That would be true only if the A-V fistulae were largely localized to the bases. Dr. James Phillips saw a classic case at the University of Arkansas. The patient had a single, large pulmonary A-V fistula located in the apex of the left lung. The major drop in Pa_{O_2} occurred when the patient was placed in the Trendelenburg position and improved greatly when the patient sat up (personal communication).

DR. CUMMISKEY: In the Trendelenburg position, there was the greatest shunt? How about the supine compared with the upright?

DR. ROBIN: I do not believe Phillips carried out studies in this case with the patient in the upright position.

DR. CUMMISKEY: Would there be a gradation going down toward the worst value when the patient was in the Trendelenburg position?

TABLE 1.—*Changes in Blood Gas Values and Shunt With Changes in Position and Exercise. Note Progressively Severe Orthodeoxia With Changes From the Supine to Standing Position*

	pH	Pc_{O_2}	Hc_{O_3}	Po_2	FiO_2
Supine	7.46	31	21.9	61	room air
Standing for 10 minutes	7.45	30	20.8	50	room air
Exercise (6.5 minutes at 3.5 mph, slope 5 percent)	7.38	27	15.9	48	room air
Sitting for 20 minutes after exercise	7.44	29	19.6	55	room air
Shunt Study with Positional Changes					
Supine	7.46	27	18.8	273	100%
Sitting	7.44	29	19.3	120	100%
Standing	7.44	29	19.5	78	100%

DR. ROBIN: The standing position is really different than the sitting position, and I prefer to discuss that later. In some of the cases that Dr. Goris and I studied, for example, there was an additional further fall in oxygen pressure when patients stood, compared with when they were sitting. This suggests that it is not only gravitational effects on shunt flow that determines the Pa_{O_2}.

DR. CUMMISKEY: We also studied the effects of exercise on the patient. The Pa_{O_2} fell a little further on exercise, though not significantly. After sitting for 20 minutes after exercise, the Pa_{O_2} was 55 torr. We then carried out a 100 percent oxygen study: in the supine position the Pa_{O_2} was 273, in the sitting position it was 120 and when she stood up it was 78 torr indicating a large shunt that increased progressively from supine to sitting to standing (Table 1). Dr. Robin, would you comment on these data?

DR. ROBIN: The changes in Po_2 and shunt are so large that they must reflect true alterations in oxygen exchange. Decreased oxygen saturation in the upright versus supine position has been called orthodeoxia.[3] It should be emphasized that calculations of shunt without determining the value of mixed venous oxygen under these conditions are not accurate. Changes in position may well cause changes in cardiac output and influence mixed venous oxygen saturation. Technically, therefore, the shunt calculations are not satisfactory. Moreover changes in position may affect both the volume of flow through the shunt as well as the oxygen content of the blood flowing through the shunt. The findings in this case show the development of true orthodeoxia. This can be explained by preferential increase in shunt flow.

However, the further decrease in oxygen pressure in the standing position cannot be so explained. One possibility is that standing is associated with loss of fluid into the tissues leading to a fall in cardiac output, reducing mixed venous oxygen content which then reduces Pa_{O_2} because of the reduced oxygen content of mixed venous blood going through the shunt vessels.[4]

DR. CUMMISKEY: At that stage, then we went on to do a lung perfusion scan with whole body counting in the standing position. This showed a shunt of 35 percent of the cardiac output.

DR. ROBIN: Dr. Goris, what we would really like to come out of this conference, among other things, is an appreciation for the errors in estimating shunts by whole body scanning compared with say, the 100 percent oxygen method or the West-Wagner multiple inert gas method.

DR. GORIS: We use microspheres made of albumin labeled with technetium 99m. The tracer, whose size is in the range of 35μ, is trapped in the pulmonary capillaries. We do know that in patients without vascular shunts, 95 ± 3 percent of the tracer remains in the lung. If a larger fraction goes to the systemic side, one assumes that the tracer found a larger arteriovenous connection. By quantitating extrapulmonary radioactivity, a shunt can be calculated.[6]

DR. ROBIN: Do you have any independent way of determining the size of the particles? How much small *tail* do you have?

DR. GORIS: If you look at the tracer we have used, you would have 5 percent, which would be less than 15μ, and not many particles larger than 60μ.

DR. ROBIN: And of that 5 percent material of small tail would it be close to capillary size or is a substantial fraction below 8μ?

DR. GORIS: There is a certain amount of slough that we cannot eliminate. We know that in most patients in whom there is no suspicion of any kind of shunt, not many spheres go to the systemic circulation.

DR. ROBIN: Clinically, therefore, we cannot distinguish between two processes: labelled particles which are small enough getting through the capillaries and that fraction of the cardiac output that normally goes through anatomical shunts.

DR. GORIS: It is just a coincidence that the calculations happen to correspond so well with calculations based on physiologic methods. Given a patient with a certain body volume but a variable body geometry, the lungs and the body generally contain radioactive particles that are emitting gamma rays. Some of the gamma rays never escape because they become trapped within the body as a result of absorption of the tracer. Quantitating gamma ray emission is not the same process as liquid scintillation counting of a very small sample whose geometry and absorption are tightly controlled. In fact, we do not even know for certain that we count the top portions of the patient with the same efficiency as we count the lower portions.

DR. ROBIN: I would like to ask an additional question. If you are just looking at the lung, how deep within the lung do you suppose you see with a ventilation scan? And how deep do you see in a perfusion scan? My impression is that with xenon (either 127 or 133) you are looking at an outer shell of lung tissue because of internal absorption. Perfusion scans in which you use higher energy provide deeper representation of the lung compared with ventilation scans. Are these fair questions?

DR. GORIS: Those are very fair questions. The absorption is important. The average patient does have a certain amount of fatty tissue and muscle and bone surrounding the lung. Because of internal absorption, which is more important for xenon 133 than for technetium 99m, activity in superficial tissues is relatively better detected with technetium 99m.

DR. CUMMISKEY: Does that mean that in a fat person the results are different than in a thin person?

DR. GORIS: Yet, it does. Absolutely.

DR. ROBIN: So, you make another assumption that is open to question: you assume the absorption is homogeneous. That is fine from the standpoint of homogeneity of one lung versus the other, but it is not so good in looking at regional changes. Is that a fair statement to make?

DR. GORIS: That is correct. Now one of the advantages of krypton 81m used for ventilation scanning is that the energy is exactly the same or very close to the same as the tracer that is used

for the perfusion scan (technetium). Comparison between the two would be more exact.

To go back to the detection of right-to-left shunting, in a patient without a shunt, activity is detected in the lung only, and not in the body, because 95 percent of the tracer sticks in the lung. In the patients whom we are discussing, you see a large amount of body, and the kidneys on the image representing the activity distribution. (If you do not recognize the kidneys as individual structures, there is something peculiar going on; either the patient does not have normal kidneys or your tracer is not behaving properly.) In the case of a shunt, the kidneys should be seen very well, since they get 15 percent of the cardiac output. When I look at the perfusion scan with the computer, I have to select the region that I will call the lungs. Even if some extrathoracic regions are included, the error is not large because even when only 50 percent radioactivity remains in the lung (and 50 percent in the rest of the body), a large fraction of the other 50 percent would still not be included by making the lung region too large. I think that I have now reviewed three types of error: (1) transposing 1:1 an anatomic observation into a physiological one (for example, that larger vessels are shunting vessels), (2) assuming that the tracer is homogeneous and distributes itself according to blood flow and (3) assuming that the measurements are based on an accurate recognition of anatomical regions that are uniformly detected.

Dr. Robin: Can I ask you about one of the errors? Could filtering be used to eliminate at least the tail of small particles in order to have more homogeneous microspheres?

Dr. Goris: Yes, we could do that.

Dr. Cummiskey: Does not the manufacturer say that 95 percent of the microspheres fall between 15 and 35μ?

Dr. Goris: Yes, something like that. From each individual batch they take only one sample which they check and then decide whether it passes muster. You would have to check each dose yourself.

Dr. Robin: It would be inconceivable to me that you fill all of the pulmonary precapillaries with particles that were 35μ in diameter and that the patient would survive. So the truth of the matter is that you only count a fraction of the capillaries.

Dr. Goris: It is estimated as one in 10,000. The total number of spheres varies between 100,000 and 600,000.

Dr. Robin: That estimate seems overly precise. How was it obtained? Has anyone carried out studies in animals to determine how many of the gas exchange units in the lung are being occluded by tracer particles?

Dr. Goris: Yes, studies in dogs have been done using continuous infusions and determinations of oxygen saturation at the same time. Before you can measure alterations of gas exchange in the lung, you have to inject much more tracer than we do.

Dr. Robin: So there is no quantitative estimate of what fraction of the gas exchange units within the lung are being seen with a perfusion scan?

Dr. Hance: It must vary remarkably depending on how sick the patient is.

Dr. Goris: Yes, that is correct. Some patients are seen who are known to have very low oxygen saturation values. In these patients injection is done while we watch the distribution of the tracer because of two reported cases of death in patients with massive lung disease who had only a very small part of their lung perfused. In children and also in adults who appear cyanotic we do not inject the usual amount but dilute the tracer by another factor of ten because we do not want to embolize the brain.

Dr. Theodore: Basically, therefore, if you got further and further into the chest, then you would have a difference in terms of the ratio of counts.

Dr. Goris: That is absolutely correct if two tracers with different emission energies are used.

Dr. Robin: When I read the original paper proposing ventilation scanning for the diagnosis of pulmonary embolism (incidentally, the first one came from Stanford[6]), my reaction was that aside from physiological problems, the approach was unrealistic because of the counting problems that you point out. Intuitively it seemed that it would be most difficult to look at a thin rim of tissue and try to make specific correlations between the anatomy and the counting. Specifically I thought that major decreases in ventilation might not be detected. Is that unfair?

Dr. Goris: No, it is not unfair. We were so much

aware of the problems that at one time we used xenon for both the ventilation and the perfusion in order to have at least the same type of physical restrictions, because comparison is the key.

DR. ROBIN: How do you go from the raw data to the results provided as Polaroid pictures?

DR. GORIS: The instrument we use has an oscilloscope. The detector detects a little flash on the oscilloscope screen in view of a Polaroid camera whose shutters remain open. The problem is calibration. You cannot really use this Polaroid image to decide whether the shunt is large or not, only to illustrate a shunt.

DR. PINSKY: So, can you subtract from the Polaroid picture?

DR. GORIS: No. Simultaneously the data are stored in a computer which is used for quantitation.

DR. CUMMISKEY: The second patient this morning is a 56-year-old man who presented with a brain abscess in 1969. In 1973 he was admitted with dyspnea at rest and increased sputum production. An x-ray study of the chest showed numerous nodules throughout the lung fields. A pulmonary angiogram at that time showed large A-V fistulae in the right and left lower lobes. Both these fistulae were resected with a minimum loss of lung tissue. A pulmonary angiogram done in the Palo Alto Veterans Administration Medical Center four years later showed these lesions to be absent and no other fistulae were noted. Pulmonary function tests and blood gas studies were done after surgical operation and showed hypoxemia and obstructive lung disease.

DR. ROBIN: So now after operation there is no evidence of an anatomical pulmonary vascular shunt by angiography or by scan. However, the patient is hypoxemic. This case suggests a new use for the Goris scan. As people get older, and especially if they are smokers, intrinsic lung disease develops. That must also be true of those persons who have pulmonary A-V fistulae. By using the Goris scan you could distinguish between patients with persistent vascular shunts and those with intrinsic lung disease and alveolar shunts.

DR. THEODORE: Would you discuss that further?

DR. ROBIN: One of the important things about the concept that there are three kinds of shunt—alveolar shunts caused by lung disease, pulmonary vascular shunts and cardiac shunts—is that they require quite different forms of therapy.[7] I have previously thought statically about these patients. You find one category of shunt or another in a patient and the patient remains in a given category indefinitely. The data from the second patient illustrate that one must consider the possibility of change with the passage of time. Let us say that a 35-year-old patient has a pulmonary vascular shunt documented by a Goris scan plus other data, and that you treat the patient successfully. The patient is a smoker and is subject to the same kinds of things that happen to lungs with aging and smoking. Later an alveolar shunt may develop. When the patient returns hypoxemic, you say "Oh my God, we didn't remove all of the pulmonary A-V fistulae and, therefore, we're going to angiogram the patient and look for resectable areas." Whereas an independent disease has developed.

DR. CUMMISKEY: And that was the interpretation in this patient in October 1977.

DR. LYNNE-DAVIES: His referral originated with a phone call: "We have a man here who is known to have the Rendu-Osler-Weber syndrome. He has had previous surgical therapy for it. He did well for a while, and now is much worse. We suspect he has other fistulae which must be resected." He was referred to us and the end results of the workup, in terms of the original disease, were negative. The management, therefore, was substantially different. Treatment for chronic bronchitis was required.

DR. CUMMISKEY: Now, if we can just go back to the first patient. The issue really is whether to reoperate to remove additional A-V fistulae. We ask "Should she be considered now for a pulmonary angiogram with a view to possible operation?" Or should we take the opinion of 1972, and say "Well, that is probably the way it still is five years later."

DR. ROBIN: I think the answer to that is easy. We should obtain the angiograms of 1972 and see. If these were technically satisfactory, then I think you have to assume that the hypoxemia relates to the known pulmonary vascular shunts. In addition, our studies suggest that the A-V malformations account for most of the hypoxemia now. Now, the question of whether it is surgically

approachable or not depends on what the previous angiograms showed. If we do not have those data or the material is not obtainable, then we ought to determine that we have little to offer except an operation. The focus of the clinical management is on that critical information: What did the old angiograms show? If they showed inoperability, then we have no right to have new angiograms made. However, if the angiograms are not available then we have to know whether there is potentially resectable disease. Simply getting new angiograms without trying to obtain the old ones is not acceptable. Pulmonary angiograms are dangerous and have their own inherent problems.

DR. CUMMISKEY: Perhaps some of those A-V fistulae of 1972 have opened up and now may be possible regions for excision?

DR. LYNNE-DAVIES: If by any standards they were inoperable in 1972 and since then have gotten worse, that really does not affect the issue of management. On the other hand, if the studies from 1972 are either unobtainable or unsatisfactory for any reason, we do not sufficient information. Clearly, we would have to go ahead and obtain the essential information.

DR. CUMMISKEY: Except it seems now that you are taking an opinion for a fact; that is, the operability of the lesions.

DR. ROBIN: We either have to get the 1972 angiograms and look at them ourselves, or we have to get new ones. But the first thing to do is to try and obtain the earlier data.

DR. CUMMISKEY: And now a second question: Is there any place in a case like this or in other cases of pulmonary A-V fistulae, for doing selective injections into the areas of the fistulae? What is the state of the art on that?

DR. ROBIN: You mean to try to obliterate them?

DR. CUMMISKEY: Yes, obliterate them.

DR. ROBIN: I think it would be very dangerous. But my answer is that I do not know.

DR. CUMMISKEY: Then the third thing, of course, is that this patient should probably be given oxygen.

DR. ROBIN: Yes, I would like to discuss that in a moment.

DR. THEODORE: That raises some questions too.

DR. GORIS: I would like to mention a small point: If your surgeon now looks at the old data, he then has an answer whether he would have operated based on that information. If one of those lesions has now become three times as large, then it is not only a question of technical feasibility but how "attractive" it looks to him.

DR. ROBIN: But we would have a voice in making that decision. In this type of case there is little accumulated experience. Our surgeon may look at the angiograms and indicate one large fistula and say "I feel confident that I should operate." And I may look at it and say "Yes, but look at the other 98 lesions. As you remove more lung tissue, you are going to increase pulmonary vascular resistance and the other ones are going to get larger. I do not think you should operate." Then we would reach some consensus based on best guess on how to manage the patient.

What I would like to do now is to indicate some of the questions that are unanswered in patients who have pulmonary vascular shunts. It is more or less settled that determining the difference between alveolar shunts and pulmonary vascular shunts can provide important information. One simple thing that we do not know is the prevalence of pulmonary vascular shunts. No one has any idea of the frequency of the occurrence of pulmonary vascular shunts in various patient populations. The general view until now has been that pulmonary vascular shunts are uncommon. Clinically important pulmonary vascular shunts were essentially limited to two circumstances: (1) the Rendu-Osler-Weber syndrome and (2) sporadic pulmonary A-V fistula, unassociated with either a hereditary component or with A-V fistulae occurring elsewhere in the body. At present we do not even know the prevalence of A-V communications in liver disease. It is to be hoped that, over the course of the next two years, Drs. Salfen and Rushing will give us a better estimate of how common this is in liver disease. There are a number of other disorders in which it is reasonable to speculate that significant pulmonary vascular A-V shunting is present. One of these is pulmonary hypertension. Patients with severe primary pulmonary hypertension not uncommonly have substantial degrees of hypoxemia—not easily accounted for by abnormal parenchymal lung function. In some of these

patients, hypoxemia develops as a result of right-to-left shunting in the heart, say through a patent foramen ovale. In other patients, who seem to have substantial degrees of hypoxemia, that explanation is not tenable, at least judging by angiographic or catheterization studies. If the Goris scan can provide insight into prevalence, then it would provide an important addition to our understanding of pulmonary hypertension.

DR. HANCE: However, these patients would be at increased risk from perfusion scanning.

DR. ROBIN: You would have to try to estimate the possible value of the procedure against the possible risk in individual patients. All I am saying is that cardiac catheterization and angiograms have a greater risk in all probability than perfusion scanning. The second group of patients who often have hypoxemia, the mechanisms of which are not completely defined, are patients with pulmonary embolism.* There are two possibilities to explain the development of direct A-V communications in these patients. One, which was first raised at least 35 years ago, is that in the normal lung there may be direct A-V communications. The reason that these are not the sites of shunting is that the pressure relationships are such that blood flow through them is small in normal persons. Now, with pulmonary embolism, shunts might open up not de novo, but because of a new set of pressure-volume flow relationships within the lung vasculature. The second possibility is that somehow with acute pulmonary hypertension, new vascular shunts develop. The third disease (or group of diseases) in which there is occasionally hypoxemia not explained easily by the kind of measurements commonly available is pulmonary carcinoma or, more accurately, pulmonary malignant lesions. Work conducted by Folkman suggests that there are humoral agents elaborated by tumor cells (capillary angiogenic factors) which cause the development of new vessels.[8]

I have seen two patients who were shown to have substantial A-V communications within the lung. One had Hodgkin disease of the mediastinum and the other had bronchogenic carcinoma. Each had hypoxemia of unknown cause. The basis of the abnormal A-V communications was not clear.

*The major mechanism is known. It is the development of regional hypoventilation in areas that are perfused.

DR. HANCE: Demonstrated by?

DR. ROBIN: Demonstrated during surgical procedure. I would speculate that with some tumors, important A-V communications may develop in the lung, and the possibility of vascular shunts should be considered in patients with hypoxemia of unknown cause.

A second important problem involves the regulation of lung shunt vessels; that is, determining the physiological mechanisms that modulate pressure, volume and flow in these vessels. The amount of flow through the shunt vessel, as compared with the normal pathway, will vary as a function of the resistance through the two pathways. If, in patients who have pulmonary A-V shunts related to liver disease, one measures pulmonary vascular resistance after administering low oxygen mixtures, no increase in pulmonary vascular resistance is noted. In a normal person there is an increase in pulmonary vascular resistance.[9] The workers who showed this considered the phenomenon to be a "failure of pulmonary vasoconstriction." In other words, as alveolar oxygen pressure decreased in patients with pulmonary vascular shunts, you did not evoke whatever it is that produces pulmonary vasoconstriction and, therefore, pulmonary vascular resistance did not increase. Having analyzed their data I think they show that as you lower Pa_{O_2}, by administering low oxygen mixtures to breathe, you vasoconstrict normal pulmonary arterioles. This increases flow through the low resistance shunt vessels and pulmonary vascular resistance is not increased. Therefore, I believe it is probable that there is a mechanical rather than a chemical explanation for failure of pulmonary artery pressure and pulmonary vascular resistance to rise.

One important physiological question is what happens then to the resistances in the normal and the shunt pathways as a result of low alveolar oxygen tensions. Another is whether it is possible that these communications actually respond to physiologic and pharmacologic stimuli like systemic vessels rather than pulmonary blood vessels? As you know, in systemic vascular beds, if you drop the oxygen pressure vasodilatation occurs. Is it possible then that as you drop alveolar oxygen pressure, you are not only vasoconstricting normal vessels, but you are vasodilating the shunt vessels? Should it turn out that the shunt vessels do act like systemic vessels, then is it possible that they respond like systemic ves-

sels to other kinds of pharmacological agents like beta-adrenergic-agonists and alpha-adrenergic-agonists. By administering these agents could you selectively produce vasoconstriction of the shunt vessels and, therefore, force more blood through the normal pathway? Even if the beta agonists increased resistance in both pathways, but selectively increased resistance more in shunt vessels than in normal vessels, you could decrease the volume of shunting in the patient, and improve gas exchange. The whole question of the response of shunt vessels to pharmacologic agents, as well as to oxygen, is an important one.

In the first patient, it might be useful to maintain alveolar oxygen pressure at the highest levels possible. Maintaining a high oxygen pressure might prevent, in many regions, alveolar hypoxia and, therefore, would tend to keep the resistance in the normal pathway as low as possible. A trial of oxygen administration during the time she sleeps might be warranted for this purpose.

DR. HANCE: We have no reason to think that her alveolar P_{O_2} is low, though. It is not in a range in which oxygen therapy normally would be needed.

DR. ROBIN: That is only mean alveolar P_{O_2}. We do not know what is happening regionally.

DR. HANCE: But we have no reason to suspect that it is bad.

DR. LYNNE-DAVIES: There are two aspects to it. I think that, as far as the shunt you have discussed, one can speculate on two or three things. First, it must be behaving differently than the others because it is a shunt vessel, and presumably exposed to much lower oxygen pressures going into it and coming out of it than vessels in the main transit. On the other hand, you might be right that it is behaving like a systemic vessel. An alternative possibility is that it is maximally vasoconstricted and is behaving like a pulmonary vessel. It could still have the same controlling mechanisms but, because throughout its course there is a continuously low oxygen tension, it might behave much differently.

DR. ROBIN: I am making the assumption that vasoconstriction does not take place in the capillary but in precapillary vessels, and that the normal vessels, precapillary vessels and shunt vessels are exposed to a low oxygen pressure.

DR. HANCE: But in the patient who has a normal alveolar oxygen level, the blood coming into the pulmonary capillary is low in oxygen.

MR. VAN KESSEL: Are you postulating that the shunt is proximal to the constriction? In other words, there would be a difference whether or not the shunt vessel with vasoconstrictors is a matter of hypoxemia or whether or not the shunt would take off proximal or distal. That could still be right, depending on where you place the shunt.

DR. LYNNE-DAVIES: I agree with Dr. Hance, in a sense, about high alveolar oxygen pressure in areas adjacent to the normal vessels. However, I am not quite sure, taking your model, how increasing it would alter vascular resistance.

DR. ROBIN: Suppose, for example, that by using high oxygen you increase her mixed venous oxygen pressure from 40 to 50 or 55 torr. Now, the control of these vessels, if they are systemic vessels, will not depend on what is happening to alveolar oxygen pressure. It will depend on what is happening to precapillary oxygen pressure. High oxygen tensions do vasoconstrict systemic arterioles. High oxygen tensions probably vasodilate pulmonary precapillaries. I would be delighted to improve arterial oxygen pressure by any combination of shunt vasoconstriction and pulmonary vascular vasodilatation.

DR. LYNNE-DAVIES: Even if we accept the first two possibilities, it then seems to me that you said "Well, let's see how she does with oxygen at night and so forth." Looking at the blood gas values, the most crucial time for her to get oxygen would appear to be when she is standing up.

DR. ROBIN: Do you consider that your objections, which are more or less theoretical, are sufficiently strong in your mind so that you would not try oxygen?

DR. LYNNE-DAVIES: No, they are not sufficiently strong that I would not try oxygen.

DR. ROBIN: Perhaps a summary of the conference might be worthwhile. We have discussed two cases of patients with pulmonary A-V communications. The first teaches us that these communications may be so large and diffuse that curative surgical procedures may not be possible. The second teaches us that even after curative surgical therapy, the patient is not immune to the

development of more common forms of lung disease. This may be mistaken for a recurrence of A-V communications.

We have also discussed a number of other points: (1) the application of Ockham's razor to clinical medicine, (2) the causes of cerebral disease in patients with right to left shunts, (3) the effects of position and exercise on gas exchange in the lung, (4) the use of the Goris scan in detecting and quantifying the lung vascular shunts, (5) the technical limitations of ventilation and perfusion lung scanning, (6) therapeutic approaches to pulmonary A-V communications and (7) the physiological regulation of shunt vessels in the lung.

REFERENCES

1. Tetalman MR, Hoffer PB, Heck LL, et al: Perfusion scans in normal volunteers. Radiology 106:593-594, Mar 1973

2. Gomes MR, Bernatz PE, Dines DE: Pulmonary arteriovenous fistulas. Ann Thorac Surg 7:582-593, Jun 1969

3. Robin ED, Laman D, Horn B: Platypnea related to orthodeoxia caused by true vascular lung shunts. N Engl J Med 294: 941-943, Apr 22, 1976

4. Robin ED: Dysoxia, chap 14, *In* Rubenstein E (Ed): Respiratory Diseases in Scientific American Medicine. New York, Scientific American, 1978

5. Robin ED, Horn B, Goris M, et al: Detection quantitation and pathophysiology of lung "spiders." Trans Assoc Am Phys 88: 202-216, 1975

6. DeNardo G, Goodwin D, Ravasini R, et al: The ventilatory lung scan in the diagnosis of pulmonary embolism. N Engl J Med 282:1334-1336, Jun 11, 1970

7. Robin ED, Laman D, Goris ML, et al: A shunt is (not) a shunt is (not) a shunt. Am Rev Resp Dis 115:553-557, Apr 1977

8. Day SB, et al: Cancer Invasion and Metastasis—Biologic Mechanisms and Therapy. New York, Raven Press, 1977

9. Daoud FS, Reeves JT, Schaefer JW: Failure of hypoxic pulmonary vasoconstriction in patients with liver cirrhosis. J Clin Invest 51:1076-1080, May 1972

Nutritional and Metabolic Significance of End Portion of Small Bowel

A SIGNIFICANT DEVELOPMENT in recent years is the recognition that just as the proximal portion of the small bowel is essential in the matter of absorption, digestion and nutrition, so the last part of the small bowel is vital to our nutritional and metabolic status. And the last part of the small bowel is not an inert muscular tube; it is a vital structure. When it is resected for disease, there may be alterations in the recycling of bile salts and this will lead to a reduced bile salt pool. This, in turn, will interfere with absorption of fat; it will also lead to alterations in the bile salt biochemistry and lead to an increased incidence of gallstones. And so, as part of your workup, in my opinion, you should include a cholecystogram every so often, because there are at least two studies in addition to ours that suggest that there is an increased incidence of gallstones in these patients.

—JOSEPH B. KIRSNER, MD, *Chicago*

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Refer to: Ockner RK: Drug-induced liver disease—Medical Staff Conference, University of California, San Francisco. West J Med 131:36-45, Jul 1979

Drug-Induced Liver Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *The topic for this staff conference is drug-induced liver disease. Dr. Henry Kahn, the chief medical resident, will present the first case.*

DR. KAHN:† A 45-year-old white woman was admitted to hospital at the University of California, San Francisco, (UCSF) on July 19, 1978, for evaluation of jaundice. In March 1978 she had presented with fever, pancytopenia and hepatomegaly. Cultures of sputum, pleural fluid, bone marrow and liver biopsy specimens grew Mycobacterium kansasii. Before treatment, the serum glutamic oxaloacetic transaminase (SGOT) was reported at 150 U per ml, the lactic acid dehydrogenase (LDH) was 1,420 U per ml and the alkaline phosphatase was 500 IU per liter. Treatment with isoniazid, ethambutol and rifampin was begun. By June 1978 the patient's condition was clinically improved, with the following values noted: SGOT, 28 U per ml: LDH, 177 U per ml; alkaline phosphatase, 265 IU per liter, and total bilirubin 0.6 mg per dl. In July 1978 she began to note weakness, anorexia, weight loss and jaundice, and administration of isoniazid and rifampin was discontinued. She was referred to UCSF at that time.

Her past history and family history showed moderate use of alcohol, and that a cousin had disseminated Mycobacterium intracellularis. On physical examination, the patient was cachectic and afebrile, with a blood pressure of 105/80 mm of mercury and a pulse of 95. There was scleral and cutaneous icterus, a tender liver enlarged to 14 cm in span and 2+ pitting edema.

Laboratory data showed the following: leukocyte count, 5,200; hematocrit, 23 percent; SGOT, 74 U per ml; LDH, 78 U per ml; alkaline phosphatase, 137 IU per liter; albumin, 2.4 grams der dl, and hepatitis B surface antigen, negative. An x-ray study of the chest done on admission showed resolving bilateral infiltrates.

Administration of rifampin was restarted on July 19, 1978. An extensive workup was done which included a liver-spleen scan, abdominal sonogram and a computer tomography (CT) scan of the liver. These disclosed only hepatomegaly. Without the isoniazid, by July 24 the patient's SGOT level had fallen to 12 U per ml, LDH was 89 U

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†Henry Kahn, MD, Chief Medical Resident.

per ml, alkaline phosphatase was 91 IU per liter and bilirubin was 3.8 mg per dl. At that point she felt improved. On July 25, however, the temperature rose to 40°C (104°F). All routine cultures were negative; the leukocyte count fell to 2,400, and ultimately to 1,300. X-ray films of the chest showed increasing infiltrates. This was all felt to be consistent with reactivation of the underlying disease, and on August 3, because the question of isoniazid toxicity was unclear, administration of the drug was started again. On August 7 liver function tests showed SGOT to be 300 U per ml; LDH, 200 U per ml; alkaline phosphatase, 140 IU per liter, and total bilirubin, 10 mg per dl. Isoniazid administration was discontinued on August 8. Cycloserine therapy was instituted at that point. When the patient was last seen in the clinic on September 12, symptoms had improved on the regimen of cycloserine, ethambutol and rifampin. The leukocyte count remained low at 1,900, hematocrit was 34 percent and platelet count was 90,000. Liver function tests showed SGOT to be 25 U per ml; LDH, 159 U per ml, alkaline phosphatase, 140 IU per liter, and total bilirubin 2 mg per dl.

DR. SMITH: *We have a second brief case for presentation. Dr. Ann Hritz will summarize it.*

DR. HRITZ:* A 23-year-old black woman was admitted to the UCSF hospital on October 18, 1978, for evaluation of seizures, fever, pneumonia, dermatitis, hepatitis and anemia. In August 1978 she had presented at another hospital with a right upper lobe infiltrate which resolved on treatment with amoxicillin given orally. She was readmitted in September 1978 with grand mal seizures. A lumbar puncture and brain scan showed no abnormalities. She was treated with diphenylhydantoin and phenobarbital. It is of note that results of liver function tests at that time were within normal limits.

In October 1978 the patient was seen again at the other hospital for seizures, fever, exfoliative dermatitis, lymphadenopathy and hepatomegaly. The SGOT level was 544 U per ml, the bilirubin value was 4.8 mg per dl and the hematocrit had dropped from 38 percent to 23 percent without evidence of bleeding. A new right upper lobe infiltrate was noted which did not resolve on treatment with broad spectrum antibiotics.

*Ann Hritz, MD, First-year Medical Resident.

Her past medical history included atopic dermatitis since childhood and a character disorder. There had been no head trauma, hepatitis, use of drugs other than the diphenylhydantoin and phenobarbital, or ethanol abuse.

On physical examination, after transfer to UCSF, the patient was noted to be obese, with generalized erythroderma and exfoliative dermatitis. She was tachypneic with audible wheezing. Blood pressure was 90/70 mm of mercury; pulse, 120; respiratory rate, 50, and temperature, 39.9°C (103.82°F). Generalized subcutaneous edema, erythroderma and exfoliative dermatitis sparing only the mucous membranes were present. Right posterior cervical adenopathy was noted. On examination of the chest, there was at the base of both lungs dullness with decreased breath sounds. Rales were heard posteriorly over the right lung field, and there were diffuse wheezes and rhonchi. Cardiac examination showed a 2/6 systolic ejection murmur along the left sternal border. The patient's liver was tender and enlarged to 14 cm in span, and there was no evidence of splenomegaly. She was disoriented and combative. Findings on neurological examination were normal except for bilateral ankle clonus.

Laboratory studies gave the following values: the leukocyte count was 35,900 with 48 polymorphonuclear lymphocytes, 4 bands and 11 eosinophils; hematocrit, 26.2 percent; platelet count, 155,000; prothrombin time, 37.6 seconds, and partial thromboplastin time, greater than 100 seconds. A disseminated intravascular coagulation screen was negative. Results of renal function tests were normal and the blood glucose value was 43 mg per dl. The calcium level was 6.6 mg per dl; phosphorus, 0.6 mg per dl; albumin, 2.2 grams per dl. SGOT was 380 U per ml; alkaline phosphatase, 130 IU per liter; LDH, 584 U per ml, and bilirubin, 11.8 mg per dl. An x-ray film of the chest showed a left lower lobe, a right lower lobe and a right upper lobe infiltrate, and a Gram stain showed rare polymorphonuclear leukocytes with mixed oral flora.

The patient was treated with ampicillin and gentamicin and the pulmonary infiltrates resolved, although sputum cultures were not diagnostic. The dermatitis cleared after topical application of steroids. The hepatitis gradually improved after administration of diphenylhydantoin and phenobarbital was stopped. Prothrombin time also improved with fresh frozen plasma and vitamin K

administration. Findings on a liver biopsy were compatible with resolving acute hepatitis. The patient's course was further complicated by transient agranulocytosis and acute nonoliguric renal failure which resolved before discharge. There were recurrent seizures with a left temporal lobe focus, shown on an electroencephalogram, which were successfully treated with phenobarbital alone. She was discharged on November 22 without evidence of a drug reaction to the present anticonvulsant regimen. At discharge the SGOT level was 80 U per ml; alkaline phosphatase, 120 IU per liter; bilirubin 9 mg per dl, and prothrombin time and partial thromboplastin time within normal limits.

DR. SMITH: *Thank you very much. We would like to call on Dr. Robert K. Ockner to discuss these complex problems and more generally the question of drug-induced liver disease.*

DR. OCKNER:* The two cases presented illustrate very well many aspects of the common and important problem of drug-induced liver disease. It is a very difficult problem for several reasons. First, when adverse events occur during treatment with a drug for some illness, it often is unclear whether one is dealing with a reaction to the drug, an exacerbation of the underlying process or an entirely unrelated event. Second, not only are many agents in common use suspect, but every new agent that appears must be considered. Third, the matter of diagnosis is further confused by the nonspecificity of the histopathology of most drug-induced lesions; with a very few exceptions, they may closely mimic virtually all forms of liver disease. Finally, because of the tremendous number and diversity of the drugs that have been implicated and the reactions that can be seen, it is difficult to review this subject and not have it read a bit like a catalogue. To avoid this particular pitfall I briefly will review the spectrum of disorders that are associated with drug-induced liver disease, make some more detailed comments on those that are especially instructive or otherwise important for clinical or theoretical reasons, and finally comment on the two cases presented. While the lesions in these cases have histological similarities, the cases are obviously very dissimilar clinically. I reviewed this subject at these rounds about three years ago. Since that time a number of concepts that were current then have stood the test of time, but others certainly have been called into question and new concerns and problems have been raised.

*Robert K. Ockner, MD, Professor of Medicine.

TABLE 1.—*Drug-Induced Liver Injury: Clinical-Histopathological Patterns and Examples*

Zonal necrosis (acetaminophen)
Acute viral hepatitis-like reactions (isoniazid, diphenylhydantoin)
Chronic hepatitis (methyldopa)
Cholestasis
with inflammation, necrosis (chlorpromazine)
without inflammation, necrosis (estrogens)
Fatty liver
Large vacuoles (ethanol)
Small droplets (tetracycline)
Granulomata (allopurinol)
Tumors (oral contraceptives)

There are many ways to classify drug-induced liver disease. Most of the standard reference sources that deal with this topic simply list agents on the basis of their pharmacological properties—as hormones, antibiotics and the like—and then deal with the kinds of reactions that may be associated with individual drugs in each category.[1,2] That approach is particularly useful to identify the possibilities in a given case. It is perhaps less useful as the basis for today's discussion because I will review more general principles and some of the mechanisms involved. The classification I will employ is based both on histopathology and what is known (meager as it may be in some cases) about the mechanism of the injury itself. This classification is given in Table 1, and for each type of reaction one or two drugs are presented as examples.

In zonal necrosis, the first category, injury is limited to, or especially prominent in, one portion of the liver lobule. For example, central necrosis is characteristically produced by so-called *direct toxins* such as acetaminophen and carbon tetrachloride. Acetaminophen is of considerable importance clinically, and we will return to consider it at greater length. Reactions in this category are generally predictable, often dose-related, and can be produced in experimental animals. The agents of concern in the case summaries presented here fall into the category of viral hepatitis-like reactions. Unlike the first category, these agents produce necrosis which usually is focal but may be submassive or massive, rather than zonal. They are neither predictable, nor apparently dose-

related, and rather seem to depend on some kind of host idiosyncrasy, the nature of which is not well understood in most instances.

The third category, chronic hepatitis, serves as a reminder that this broad group of syndromes of chronic liver inflammation includes cases in which an etiologic role of certain drugs has been well documented; these will be mentioned briefly later in the discussion.

Cholestasis—that is, impairment of bile flow—includes two general categories: those associated with inflammation and necrosis, and those in which these features are lacking. The first group is exemplified perhaps best by chlorpromazine, and includes a very large number of other agents as well. Those forms of drug-induced cholestasis not generally associated with inflammation and necrosis are typified by the estrogens, oral contraceptives and anabolic steroids. Fatty liver also can be divided into two subcategories on the basis of the histopathology. First, there are those conditions in which fat is deposited in large vacuoles, so that the liver cell takes on the appearance of an adipocyte because of the substantial displacement of the nucleus. This is the typical appearance of fatty liver caused by ethanol abuse, as well as obesity, corticosteroid treatment and protein-calorie malnutrition. In contrast, the second group of conditions is associated with deposition of fat in small droplets distributed throughout the cell, while the nucleus remains centrally located. The classic example is the reaction caused by high doses of intravenously given tetracycline, but it is also very similar to other conditions which apparently are not drug-related, such as the Reye syndrome, obstetrical fatty liver and Jamaica vomiting sickness.

It should be noted that the most important difference between these groups with fatty liver is not so much in the histopathology, but rather in their clinical presentation. In the first group, the findings are largely unimpressive, apart from hepatomegaly and abnormal results on liver function tests, and there is no evidence that the fat in those conditions produces substantial long-term injury. In contrast, the second group is characteristically associated with a presentation that is very suggestive of massive liver cell failure and often carries a very high mortality rate. Granulomata are caused by perhaps half a dozen drugs such as phenylbutazone, phentoin, quinidine and allopurinol. Finally, hepatic tumors are included because of current concerns about their possibile relationship to oral contraceptives.

I would emphasize that the above list is not comprehensive, and certain forms of tumors and vascular occlusive processes have been excluded. Moreover, a number of drugs may cause more than one kind of reaction, while in a given patient elements of more than one kind of histopathologic change may be seen. Therefore, these categories are not necessarily rigid, specific or exclusive, either for the drug or the patient. Rather, they are intended to provide a conceptual framework.

Zonal Necrosis

Acetaminophen is of importance because it is perhaps the best understood of the agents that we will consider today. It is readily available, and has been used with increasing frequency in suicide attempts. To the extent that it succeeds, it causes a liver death, and usually requires acute ingestions in excess of 10 grams.[3] Recently, however, it has been appreciated that sustained use of acetaminophen in doses in excess of 3 grams per day may also be associated with chronic low-grade, benign and reversible liver injury.[4] The liver lesion seen in the acute cases is centrilobular necrosis, and these patients either die in the acute episode or recover completely. There is no evidence that a single exposure to acetaminophen can initiate chronic liver injury. Mitchell and his colleagues have developed much of the current information about the mechanism of acetaminophen hepatotoxicity.[3] In experimental animals it has been shown that phenobarbital, a potent inducer of drug metabolizing enzyme systems in the smooth endoplasmic reticulum, increases the rate of acetaminophen metabolism and also its toxicity. In contrast, agents that block acetaminophen metabolism are protective. The rate of metabolism of the parent compound correlates directly in those studies with covalent binding of an apparently toxic metabolite of acetaminophen to cell macromolecules, and also with the extent of liver cell necrosis. So, the concept advanced on the basis of those studies was that a toxic metabolite, rather than the parent compound, is responsible for the liver cell injury. The metabolism of acetaminophen is summarized in Figure 1. Normally a large amount is conjugated and excreted in urine, but some may be metabolized by the cytochrome P-450 dependent systems in the microsomes. To some extent the products of this latter pathway will be conjugated with glutathione and excreted

without ill effect. When large amounts are formed, however, some will react with cell macromolecules and, apparently through that mechanism, initiate a sequence that results in cell death.

Mitchell and his co-workers also have shown that as long as the cellular concentration of glutathione is adequate, the animal remains relatively protected from the effects of acetaminophen. However, as the acetaminophen dose increases, glutathione is consumed and falls to a critical level, at which the covalent binding of toxic metabolite to cell proteins increases exponentially. It should be noted that "covalent binding" per se has not been clearly established as the cause of cell injury; there are circumstances in which cells may be protected against toxic injury without an effect on covalent binding.[5] Nonetheless, this interesting concept has been useful in two general ways. First, it has provided an explanation for the threshold phenomenon in this form of toxic liver injury. Second, it suggested the possibility that if endogenous sulfhydryl groups serve a protective function, then perhaps exogenous sulfhydryl donors might be useful in the treatment of patients with acetaminophen overdosage. Of several agents that have been tested, two of the more prominently employed have been cysteamine and N-acetylcysteine. Cysteamine has been studied in greatest detail by Prescott and his associates in Edinburgh and has been the subject of considerable debate.[6] I believe it is fair to say that, despite its own substantial toxicity, the available evidence tends to support Prescott's contention that cysteamine may be protective when given early in the course to patients with significant acetaminophen overdosage. However, this interpretation is not uniformly accepted and the role for this agent remains unclear. Moreover, to the extent that cysteamine may, in fact, be beneficial, available experimental data suggest that it does not act as a sulfhydryl donor in the sense that it becomes covalently linked to the acetaminophen metabolite, but rather must act via some other mechanism, perhaps by influencing the rate of drug metabolism. At present, much more attention is focused on N-acetylcysteine, which is the subject of a national multicenter study. Results of that study are still inconclusive, but this agent has the

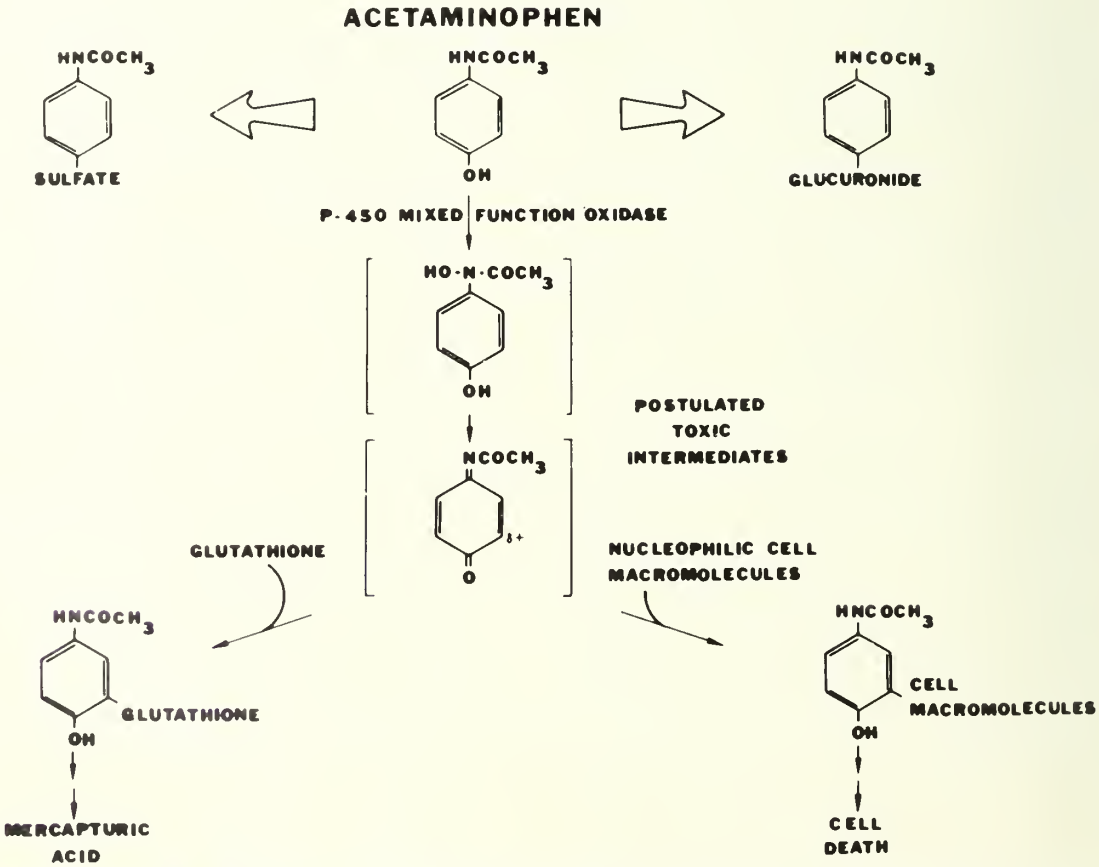

Figure 1.—Acetaminophen metabolism (reproduced with permission from Mitchell JR, and *Gastroenterology*[3]).

distinct advantage of apparently being nontoxic. There have been some favorable anecdotal reports regarding its role in the treatment of acetaminophen overdose.[7]

Chronic Hepatitis

The fact that chronic hepatitis can be caused by drugs has now been well documented.[8] Oxyphenisatin, while no longer available in this country, is available elsewhere, as an ingredient of certain laxative preparations. Other agents still in use can also cause this syndrome, including methyldopa, isoniazid, certain sulfonamides and, as mentioned, acetaminophen. Aspirin in doses in excess of about 3 grams a day may also produce continuing liver injury, perhaps analogous to that caused by chronic acetaminophen use in that both appear to be entirely reversible on cessation of therapy.[9] Alcohol can also cause a form of chronic hepatitis which is not necessarily associated with other, more typical features of alcoholism. It is important to keep in mind that these, and perhaps other drugs as yet unrecognized, should be considered in the differential diagnosis of patients with chronic liver disease.

Cholestasis

Cholestatic reactions, as noted, are of two general types. The first of these is not associated with hepatic inflammation, is entirely reversible and appears somewhat dose-dependent, and similar kinds of changes can be produced in laboratory animals. It seems likely that this reaction represents a *toxic* effect of the steroid on some aspects of liver cell function, the possible nature of which we will return to shortly. Agents which cause this form of cholestatic injury include natural and synthetic estrogens, the oral contraceptives, and anabolic and androgenic steroids which bear alpha-substituted groups at the 17 carbon of the steroid nucleus. The classical example of this reaction is seen in a few patients in whom frank jaundice develops while they are taking oral contraceptives or during the later phases of pregnancy.[10] Although the response is somewhat dose-dependent, there is an important *host* determinant of susceptibility that is not understood. It is not based on allergy, but perhaps may involve the production of unusual drug metabolites or interactions of steroids with cell membrane constituents. In some patients, these agents appear to unmask a previously inapparent Dubin-Johnson syndrome.

TABLE 2.—*Drug-Induced Cholestasis: Postulated Mechanisms and Examples*

1. Interference with specific solute transport systems (rifampin)
2. Inhibition of Na^+, K^+ adenosinetriphosphatase (chlorpromazine metabolites)
3. Alteration of membrane physical properties (estrogens)
4. Effect on microfilaments (phalloidin)
5. General interference with liver cell energy production

The second group of drugs that cause cholestasis produces an inflammatory lesion, often associated with necrosis. This category is much broader, and includes many very commonly used agents such as tranquilizers, diuretics, antithyroid agents, oral hypoglycemics and certain antibiotics. As a group, reactions tend to be less predictable, and more idiosyncratic in that they seem to depend on pronounced individual differences in susceptibility. Although this has been interpreted as suggesting that these are allergic drug reactions, this concept has not been proved. Moreover, in the case of chlorpromazine, it is recognized that among patients who take large amounts of this agent over long periods, there is a substantial incidence of abnormal findings on liver function tests, suggesting that the impairment of bile secretion may be more predictable and dose dependent than has been assumed. Evidence in support of this concept has been developed in recent studies by a number of groups. Suffice it to say that a number of derivatives of chlorpromazine have potent *direct* and predictable effects on various aspects of the bile secretory process. For many other drugs that cause cholestatic injury, the superficial appearance of *allergy* (that is, rash, fever and eosinophilia) may not be inconsistent with liver injury which is, in fact, toxic in its pathogenesis.

How is it possible for this diverse array of agents to interfere with bile secretion and, in so doing, to often mimic biliary tract obstruction? A few suggested mechanisms are listed in Table 2; there are others as well. It is possible that some agents may interfere with specific solute transport systems. For example, there is evidence in man and experimental animals that rifampin has a direct and reversible effect on hepatic uptake processes, possibly mediated at the cell membrane. A number of agents interfere with the function of liver cell membrane Na^+, K^+ adenosinetriphosphatase. The nature of the relationship

of this enzyme to bile secretion is still a matter of investigation, but it has been shown to be sensitive to agents that are associated with cholestasis. Estrogens and other agents have been shown to alter the physical properties of the membrane, usually associated with changes in fluidity. Recent evidence in regard to phalloidin, a toxin in the poisonous mushroom Amanita phalloides, has shown that this agent interferes with normal microfilament function, and it has been suggested that it may cause cholestasis experimentally through its effect on cytoskeletal elements. Finally, a cholestatic syndrome can result from a very nonspecific interference with cell energy production. Although not a drug-related phenomenon, it is worth mentioning that in patients in whom the liver has been severely anoxic—for example, in cases of prolonged hypotension or severe congestive failure—a frankly cholestatic syndrome resembling bile duct obstruction may occur. This suggests that a very nonspecific injury may also profoundly impair bile secretion, implying that this particular response to liver injury may represent a final common path through which a wide range of seemingly unrelated influences may exert an adverse effect.

Hepatic Tumors

The final subject that deserves some comment before we discuss today's cases is the matter of oral contraceptive-associated hepatic tumors.[11] The possible clinical significance of this has been appreciated only since the early 1970's, and recently there has been a flood of case reports and reviews of the subject. It now appears that several hundred cases have been documented, although some of those may have been reported more than once. The actual number of cases therefore is not known, but it probably does not exceed a few hundred. This suggests that we are dealing with what is probably a very rare complication of oral contraceptive use, although its true incidence is certainly not known at present. Most of these tumors are adenomas or focal nodular hyperplasia and, much less commonly, hepatocellular carcinoma. Most of these lesions have been seen in women who have been using oral contraceptives for more than five years, although some have been reported after shorter intervals. There is some suggestion that mestranol might especially predispose to this, but since mestranol has been in use longer than many of the other estrogenic components of the pill, that association may be entirely fortuitous.

One of the factors that makes it difficult to determine the true incidence of this complication of the pill is that it also occurs in nonusers, especially women of childbearing age, as well as in men. The tumors in these groups seem to differ, however, in that they tend to be smaller and less vascular. In a number of cases it now has been well documented that the tumors may regress when use of the oral contraceptive agent has been discontinued. Therefore, there seems little doubt that the pill either produces these lesions, or at least aggravates them.

The presentation of these lesions in a substantial number of cases is dramatic and unexpected. Many present catastrophically, either as hemorrhage into the tumor or into the free peritoneal cavity. This is especially the case with adenomas. Others, especially focal nodular hyperplasia, are discovered only incidentally at laparotomy done for unrelated reasons. The number that are detected by careful physical examination or on the basis of more mild symptoms is small. Moreover, routine liver function tests are disappointingly insensitive, so that more invasive, costly or dangerous tests would need to be employed to detect these lesions with any degree of sensitivity in asymptomatic persons. Obviously, any serious attempt at surveillance would require substantial expense and possible adverse effects, and would not appear to be appropriate. Because of the apparent rarity of these lesions, the priority, as Klatskin has suggested, is to better document its true incidence and to identify other possible etiologic factors rather than to embark on any widespread efforts at screening patients taking oral contraceptives with regard to the possibility that they may have an undiscovered tumor.

Viral Hepatitis-like Reactions

At this point, I would like to turn to the hepatic reactions that resemble acute viral hepatitis and which are exemplified by our two patients today. In addition to isoniazid and phenytoin sodium, this lesion is produced by a number of drugs, including halothane and certain sulfonamides. It is a very important problem for two reasons. First, these reactions are neither predictable nor apparently dose-related, yet unlike most of the other conditions we have discussed, they may often lead to death. Second, they make up a spectrum in themselves in regard to clinical

presentation, which is strikingly shown by the two cases presented in this conference.

Diphenylhydantoin hepatitis has been the subject of some 20 case reports, in a large percentage of which the patients died.[12,13] This undoubtedly reflects some selection so that neither the true incidence of the disease or its prognosis is known. Among the cases reported there does appear to be a somewhat increased incidence among blacks, but again the validity of that impression is not clear.

The first case discussed here fits the general characteristics of the reported cases. The timing of the onset of disease in this patient was entirely consistent with what has usually been observed (that is, two to six weeks after initiating treatment), and she presented with features which suggested an allergic reaction, including erythematous maculopapular eruption, arthralgias and arthritis, fever, lymphadenopathy and a very high eosinophil count. Also, the total leukocyte count was very high, a common observation among the reported cases. The results of liver function tests were abnormal, consistent with an acute hepatic injury; a feature common to many of the reports is a very high prothrombin time. The biopsy findings were entirely consistent with an acute hepatitis-like reaction. The mechanism of this injury is not understood. As noted, the clinical features suggest an allergic reaction and there has been evidence for a circulating antibody to phenytoin sodium in a few of these cases. Its role in pathogenesis is not known, and the mechanism of the liver injury is quite unclear. For example, in several reported cases, patients have been rechallenged with phenytoin sodium after their illnesses have subsided. In these cases, the features of their *allergic* presentation were reproduced by this maneuver, including rash, fever, eosinophilia and sometimes the adenopathy. However, in no case to my knowledge did rechallenge cause any change in liver function. Second, a number of studies have shown that among groups of patients taking this agent for long periods, there is an increased incidence of abnormal results in liver function tests, again suggesting a possible toxic mechanism. In any case, this patient's outcome has been generally favorable. The biopsy features do not imply a chronic hepatitis or other progressive liver injury. The patient had what seemed to be an inappropriately high bilirubin level at one point in the course, and there was a level of 60 mg per dl at a time when clinical improvement

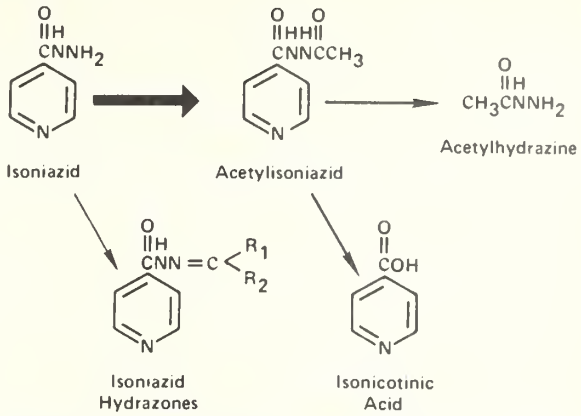

Figure 2.—Metabolism of isoniazid (reproduced with permission from Mitchell JR, and *Ann Intern Med*[14]).

was occurring. There appears to be no obvious single explanation for this. One can only assume that this represented a multifactorial phenomenon, in which residual liver dysfunction, a low-grade hemolysis and some degree of azotemia interfering with the excretion of conjugated bilirubin may all have played a role.

The second case may represent an example of isoniazid-induced liver injury, but is atypical in certain respects. It also illustrates the problem of determining whether an adverse turn of events in a patient's course is due to the disease being treated or to the treatment being used. The seriousness of the infection in this case required certainty about whether isoniazid was indeed toxic. Although rechallenge with isoniazid should generally be avoided, this was an unusual situation that I believe justified the decisions that were made. Usually, the presentation of clinically apparent isoniazid hepatitis is similar to that of viral hepatitis.[14] It is almost never associated with the *allergic* features that characterize phenytoin hepatitis. The onset is usually early, within the first two months, but may occur as late as 12 months. In contrast to phenytoin hepatitis, the incidence of isoniazid hepatitis consistently approximates 1 percent. Also, it is highly age-dependent: among persons younger than 20 it is very rare, rising to about 2 percent among patients older than 50. The reason for this age dependency is not understood. The mortality rate has varied, but is substantial, much higher than for ordinary viral hepatitis, and ranges between 10 percent and 20 percent.

In an earlier study, analyses were done in a group of survivors of isoniazid hepatitis with respect to acetylator phenotype—that is, the rate

at which isoniazid was acetylated (inactivated). From that study it was found that patients with rapid acetylators were disproportionately represented among this group, and it was concluded that they were at increased risk of development of isoniazid hepatitis. This conclusion was quite consistent with the general concept that a toxic metabolite of isoniazid might be responsible for the injury, based on what was known about the drug's metabolism (Figure 2). Isoniazid is first acetylated in the liver, and is thereby inactivated in regard to antibacterial effect. It then is hydrolyzed, and one of the important reaction products is monoacetylhydrazine which is generally accepted to be a potent hepatotoxin. Presumably, then, in persons with rapid acetylators monoacetylhydrazine is produced more rapidly than in persons with slow acetylators. However, the question of whether persons with rapid acetylation are predisposed to isoniazid hepatitis has been reexamined, and at present there is uncertainty about this point. This is because recent studies have shown that monoacetylhydrazine is itself acetylated, and more rapidly so by persons with rapid acetylators. Therefore, while persons with rapid acetylators produce more of the toxin they also inactivate it more rapidly to the less toxic diacetylhydrazine.[15] Consequently, it is possible that individual predisposition to isoniazid hepatotoxicity may be based on factors other than the rate of isoniazid acetylation.

It is important to realize that isoniazid also may produce changes in liver function that are subclinical. These changes differ from those associated with overt hepatitis in several respects. It occurrs in children and it is uniformly agreed that there is no relationship to acetylator phenotype. Laboratory and histological changes are mild, and reversible. The association with symptoms is inconstant, and has proved disappointing in assessing patients with regard to hepatotoxicity.[16] In general, liver function in these patients will return to normal despite continuation of therapy with the drug. The question of whether liver function tests should be routinely done in patients taking isoniazid is still controversial.

All of the studies that I have mentioned in regard to isoniazid have concerned persons receiving single drug chemoprophylaxis. There also are many studies that deal with the question of multiple drug therapy for active disease. This is a very complicated subject, and one that has been reviewed recently.[17] One agent that has received particular attention in this regard is rifampin because it has been suggested that its use is associated with a more fulminant course of hepatitis in patients who are also receiving isoniazid.[18] Current knowledge about the effects of rifampin can be summarized as follows: First, it produces a reversible impairment of hepatic uptake processes, apparently through an effect at the liver plasma membrane. Second, it is an inducer of microsomal drug metabolizing enzymes, and because of that it has been suggested that it may increase the rate of isoniazid metabolism and thereby predispose to isoniazid hepatotoxicity or increase the severity of the reaction when it occurs. Third, rifampin-associated hepatitis has been reported, but almost always in patients who are also receiving isoniazid; the incidence of truly rifampin-induced hepatitis—indeed, its existence—is unknown at present.

In conclusion, it is difficult, given this diversity of drugs and reactions, to provide generally applicable statements. Although diagnosis is probably most reliably accomplished by means of rechallenge, this approach is generally best avoided for those agents that are known to produce fatal reactions. As for the treatment of drug-induced liver disease, this primarily involves discontinuation of the suspected drug or drugs, and supportive care. I am aware of only two instances in which other forms of intervention may be beneficial. The first of these is the use of cysteamine or N-acetylcysteine in the treatment of acetaminophen overdose and, as noted, this remains controversial. The second is partial hepatic resection for oral contraceptive-associated hepatic tumors. There is no firm evidence that corticosteroids are of value in the treatment of the inflammatory viral hepatitis-like or cholestatic hepatic drug reactions, although they may be employed when systemic allergic features are particularly severe and threatening. It is clear that in this complex area substantial challenges remain, ranging from chemistry and pharmacology to clinical medicine. In the meantime we can deal best with the problem by being alert to it as an important cause of liver disease generally, and an important aspect of the continuing evaluation and management of the individual patient.

REFERENCES

1. Zimmerman H: Hepatotoxicity. New York, Appleton-Century-Crofts, 1978

2. Klatskin G: Toxic and drug-induced hepatitis, chap 20, *In* Schiff L (Ed): Disease of the Liver, Philadelphia, Lippincott, 1975

3. Mitchell R, Jollows D: Metabolic activation of drugs to toxic substances. Gastroenterology 68:392-410, 1975

4. Barker JD Jr, de Carle DJ, Anuras S: Chronic excessive acetaminophen use and liver damage. Ann Int Med 87:299-301, Sep 1977

5. Orrego H, Carmichael FJ, Phillips MJ, et al: Protection by propylthiouracil against carbon tetrachloride-induced liver damage. Gastroenterology 71:821-826, 1976

6. Prescott LF, Park J, Sutherland GR, et al: Cysteamine, methionine and penicillamine in the treatment of paracetamol poisoning. Lancet 2:109-113, 1976

7. Prescott LF, Park J, Ballantyne A, et al: Treatment of paracetamol (acetaminophen) poisoning with N-acetylcysteine. Lancet 2:432-434, 1977

8. Maddrey WB, Boitnott JK: Drug-induced chronic liver disease. Gastroenterology 72:1348-1353, 1977

9. O'Gorman T, Koff RS: Salicylate hepatitis. Gastroenterology 72:726-728, 1977

10. Ockner RK, Davidson CS: Hepatic effects of oral contraceptives. N Engl J Med 276:331-334, 1967

11. Klatskin G: Hepatic tumors—Possible relationship to use of oral contraceptives. Gastroenterology 73:386-394, 1977

12. Lee TJ, Carney CN, Lapis JL, et al: Diphenylhydantoin-induced hepatic necrosis. Gastroenterology 70:422-424, 1976

13. Campbell CB, McGuffie C, Weedon AP, et al: Cholestatic liver disease associated with diphenylhydantoin therapy. Am J Digest Dis 22:255-262, 1977

14. Mitchell JR, Zimmerman HJ, Ishak KG, et al: Isoniazid liver injury—Clinical spectrum, pathology, and probable pathogenesis. Ann Intern Med 84:181-192 1976

15. Timbull TA, Wright JM, Baille TA: Monoacetylhydrazine as a metabolite of isoniazid in man. Clin Pharmacol Ther 22: 602-608, 1977

16. Byrd RB, Horn BR, Griggs GA, et al: Isoniazid chemoprophylaxis—Association with detection and incidence of liver toxicity. Arch Intern Med 137:1130-1133, 1977

17. Girling DJ: The hepatic toxicity of antituberculosis regimens containing isoniazid, rifampin and pyrazinamide. Tubercle 59:13-16, 1978

18. Pessayre D, Bentata M Degott C, et al: Isoniazid-rifampin fulminant hepatitis—A possible consequence of the enhancement of hepatotoxicity by enzyme induction. Gastroenterology 72: 284-289, 1977

Optimal Hematocrit

WHEN DO YOU give red cells? What is the obtimal hematocrit for a sick patient? The answer is, of course, I do not know, but there are some indications. It ought to be higher in somebody who is going to face stress on the oxygen delivering system. It should certainly be higher in somebody who has impaired hemoglobin functions so that he cannot compensate. Somebody who has been extensively transfused with old stored blood has impaired red cells, and that patient is going to require a higher hematocrit than somebody who has not been extensively transfused or who has been given fresher blood. . . .

There are possibly some situations where you might get by or might even favor a lower hematocrit. . . . The most important factor on the side of lower hematocrit is low demand. If patients are not facing a disaster, if the hemorrhage is over, if they are doing well, if they are tolerating their level of anemia well for what they are doing at the time, then for heaven's sakes leave them alone—do not transfuse them. Transfusion carries with it a significant risk. . . . If the challenge is over, and the patient is doing well, do not treat a number, treat the patient. This business of having everybody at a hematocrit of 30 because somebody says that's the right number is a silly thing. An example might be a kid who has been speared in a hockey game, is 19 years old—a young, healthy buck—has a ruptured spleen, has a quick splenectomy before the blood arrives, is awake and alert and doing very well that evening in the recovery room, asking for the newspaper, and has a hematocrit of 19. That kid should not be transfused unless you think the tie is going to come off one of your vessels, in which case you should probably reoperate and put on the damn tie properly. Do not treat numbers—treat patients.

On the other hand, let us say we have a 72-year-old woman who had a perforated diverticulum, had pus and stool all over the abdomen. She had a myocardial infarction that was known three years ago; she has an electrocardiogram suggesting several others; she's been on digitalis; she came out of a nursing home depleted, and she has an hematocrit of 32. That patient requires red cells, especially if she's having ventricular premature contractions on the monitor. Just like everything else in clinical medicine, it has to be individualized.

—JOHN A. COLLINS, MD, *Palo Alto, California*

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Important Advances in Clinical Medicine

Epitomes of Progress—Chest Diseases

The Scientific Board of the California Medical Association presents the following inventory of items of progress in chest diseases. Each item, in the judgment of panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in chest diseases which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Chest Diseases of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Asbestosis

ASBESTOSIS is a pneumoconiosis resulting from the inhalation of asbestos particles, and manifested by diffuse interstitial fibrosis of the lung and fibrotic reactions of the parietal pleura. It is found predominantly in workers directly involved with asbestos, such as miners, millers of asbestos, shipyard workers and insulation workers. There are, however, more than 4,000 known uses of asbestos fiber and production has risen from 50 tons in 1877 to over 4 million tons in 1970. It is prudent for clinicians to become familiar with common work-classifications and industries associated with exposure to asbestos. There is also an estimated emission into the environmental air of 50,000 tons per year with emission in California (in 1966) of about 1,500 tons. Asbestosis has even been diagnosed in nonoccupational groups, particularly in household contacts of asbestos workers and also in groups living near asbestos production or use sources.

In addition to producing pulmonary and pleural fibrosis, it has been strongly associated pathologically with bronchogenic carcinoma, with mesotheliomas of the pleura and peritoneum, and probably with some gastrointestinal cancer. Physiologically, it has resulted in restrictive manifestations, decrease in gas transport measurements and some small airways dysfunction, with subsequent development of cor pulmonale.

It is of particular concern that clinical manifestations of asbestosis as well as malignant sequelae may not become evident for more than 20, 30 or 40 years after exposure. Malignancy in persons who worked in shipyards during World War II, many of whom reside along the West Coast, is just now becoming evident. Bronchogenic carcinoma is less usual in nonsmokers exposed to asbestos. In persons exposed to both asbestos and cigarette smoking the risk of cancer is significantly greater than additive. Those workers who have been exposed to asbestos fibers must be emphatically warned that smoking is an *extreme* hazard for them.

Symptoms of asbestosis do not differ from those of diffuse interstitial fibroses caused by other etiologic agents. Early breathlessness on exertion progresses to increasing dyspnea, even at rest. Cough is common with or without sputum and is often croupy in nature. Associated bronchitis from concomitant smoking is often found. Physical findings usually show somewhat characteristic crepitations on auscultation of the lower lung fields and less frequently in mid-lung fields. Digital clubbing is frequent. Radiographically,

the interstitial fibrosis is not diagnostic but characteristic pleural reactions are seen early. The presence of linear pleural or diaphragmatic calcifications should alert one to the possible past asbestos exposure.

"Restrictive" pulmonary function measurements (reduced vital capacity, reduced maximum voluntary ventilation) are occasionally accompanied by decreased forced expiratory volumes and impaired small airways measurements. Interference with gas transport is shown by reduced diffusing capacity of the lung for carbon monoxide (DLCO) as well as increased alveolar arterial gradient for oxygen pressure, which is worsened during exercise. Carbon dioxide retention is a late manifestation.

Asbestosis should be strongly suspected when an occupational detective search is initiated in the presence of dyspnea; radiologic evidence of fibrotic, pulmonary or pleural disease decreased spirometric measurements, decreased DLCO and hypoxemia. Asbestos bodies may be found occasionally in the sputum of asymptomatic persons. Presumptive diagnoses may be confirmed by the presence of asbestos fibers in biopsy specimens of lung tissue.

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REFERENCES

Selikoff IJ, Bader RA, Bader ME, et al: Asbestosis and neoplasia. Am J Med 42:487-496, Apr 1967

Becklake MR: Asbestos-related diseases of the lung and other organs: Their epidemiology and implications for clinical practice. Am Rev Respir Dis 114(1):187-227, Jul 1976

PEEP and Barotrauma

POSITIVE END-EXPIRATORY PRESSURE (PEEP) is now widely used as a therapeutic modality for acute respiratory failure (shock lung, diffuse capillary blood syndrome and respiratory distress syndrome). PEEP reduces shunt by preventing atelectasis, the primary cause of hypoxemia in this syndrome. This is accomplished by the associated increase in functional residual capacity (FRC). PEEP may also reduce shunt by discouraging the accumulation of alveolar and interstitial edema fluid. Improvement in the distribution of ventilation with PEEP has also been noted, which may be related to improved airway patency accompanying the increase in FRC as well as to alveolar recruitment with more uniform distribution of pulmonary compliance. The improvement in arterial oxygen tension with PEEP is often dramatic and permits rapid reduction in fraction of inspired oxygen (FIO_2) to safer levels.

PEEP may be accompanied by several adverse sequelae. The increase in mean transpulmonary pressure (more positive) may result in diminished venous return, and increased pulmonary vascular resistance resulting in reduced cardiac output and tissue oxygen supply. This is particularly likely with hypovolemic states although the administration of fluids in acute respiratory failure must be undertaken with great care. The use of intermittent mandatory ventilation (IMV) with PEEP or continuous negative chest pressure (cuirasse ventilator) instead of PEEP may be useful in avoiding these cardiovascular problems, although adequate respiratory support using these techniques is not always possible.

Barotrauma—including pneumothorax, subcutaneous and mediastinal emphysema—often accompanies the use of PEEP, although it is not clear whether this is more the consequence of the use of high inspiratory pressures and volumes than of PEEP itself. With preexisting hyperinflation, barotrauma is much more likely and PEEP is therefore contraindicated in obstructive lung diseases.

Appropriate and tolerable levels of PEEP are still being defined. PEEP levels of 5 to 15 cm of water are often adequate to effect a substantial improvement in hypoxemia without cardiovascular impairment or undue risk of barotrauma. These levels of PEEP have been associated with optimal static pulmonary compliance and maximum oxygen transport ("best PEEP"). In contrast, maximal improvement in shunt without detrimental effects on cardiac output ("optimal PEEP") has been noted with PEEP levels exceeding 40 cm of water. These undobutedly represent more severe varieties of acute respiratory failure in which cardiovascular effects and barotrauma are minimized because the higher pressures are not transmitted across the pulmonary parenchyma. Unfortunately in neither of the above studies was peak inspiratory pressure (and therefore degree of inspiratory inflation) controlled; therefore, it remains unclear whether PEEP alone was responsible for the improvement in oxygen supply. Nonetheless, it is probable that PEEP levels in excess of 15 cm of water may occasionally be necessary to produce optimal improvement in tissue oxygen delivery and perhaps in pulmonary compliance as well.

In practice PEEP should be limited to levels that are not associated with reductions in mixed venous oxygen tension or with serious cardiac output impedance, and which are sufficient to permit reduction of fraction of inspired oxygen to levels approximating 0.5 or less. These goals are now more readily attainable with pharmacologic car-

diovascular support based on cardiac preload and afterload assessment. The risk of barotrauma should be minimized by ensuring that increments of PEEP are not associated with increases in peak inspiratory pressure. STANLEY M. CASSAN, MD, PhD

REFERENCES

Wayne KS: Positive end-expiratory pressure (PEEP) ventilation—A review of mechanisms and actions. JAMA 236:1394-1396, Sep 20, 1976

Leftwich E, Witorsch RJ, Witorsch P: Positive end-expiratory pressure in refractory hypoxemia—A critical evaluation. Ann Intern Med 79:187-193, Aug 1973

Suter PM, Fairley B, Isenberg MD: Optimum end-expiratory pressure in patients with acute pulmonary failure. N Engl J Med 292:284-289, Feb 6, 1975

Kirby RR, Downs JB, Civetta JM, et al: High level positive end-expiratory pressure (PEEP) in acute respiratory insufficiency. Chest 67:156-163, Feb 1975

Gallagher TJ, Civetta JM, Kirby RR: Terminology update: Optimal PEEP. Crit Care Med 6:323-326, Sep-Oct, 1978

Current Status of Surgical Therapy in Lung Cancer

ALTHOUGH RESULTS of surgical resection have not changed much in the past decade, the procedure remains the best hope for long-term survival of patients with lung cancer. When patients with lung cancer are first seen the disease will be unresectable in most cases. Of patients in whom resection is thought to be curative, only a third will survive five years. For all patients in whom lung cancer is diagnosed, fewer than 10 percent will be alive five years later. The yield from surgical therapy may not have improved substantially, but physicians are now better able to decide if surgical operation, radiation therapy, chemotherapy or general supportive care should be used.

A physician seeing a patient with presumed lung cancer must answer a series of questions. First, is the lesion cancer or another disease? Various diagnostic techniques, such as tomography, can help establish the probable nature of a lesion. However, only histological characterization can definitely resolve this issue. Cytological studies of sputum, material obtained through flexible bronchoscopy or specimens obtained with percutaneous needle aspiration should yield an answer in up to 90 percent of cases. The physician must next determine if the lesion can be totally removed surgically; if residual or metastatic disease remains, death may be hastened or the quality of survival degraded. There is a rational approach to the search for metastatic lesions; not every test need be done in every patient. In about half of patients, the disease is unresectable because the tumor extends into the mediastinum. Introduction of mediastinoscopy and mediastinotomy has reduced the occurrence of exploratory thoracotomy *without resection* from about 50 percent to 10 percent or 20 percent.

In some patients, complicating diseases render the risk of surgical operation unacceptable. Inoperability due to chronic obstructive lung disease is also a frequent problem, but careful assessment of pulmonary function can help with the decision to operate or not. If after an appropriate and expeditious evaluation, all the questions are resolved in favor of operation or the lesion's true nature is still unknown, thoracotomy should be done promptly. In such cases there is a good chance for prolonged survival and this usually more than balances the risks engendered by the preoperative workup. CHARLES MITTMAN, MD

REFERENCES

Mittman C, Bruderman I: Lung cancer: To operate or not? Am Rev Respir Dis 116:477-496, Sep 1977

Selawry OS, Strauss MJ (Ed): Lung cancer. Semin Oncol 1: 161-289, 1974

Practical Applications of Wet-Mount Sputum Preparations

A COMMON DILEMMA facing physicians caring for a patient with chronic obstructive pulmonary disease is what to do when the patient's sputum turns yellow-green. Ordinarily, the physician prescribes an antimicrobial agent assuming that a respiratory infection has developed. However, one cannot distinguish an infectious from an allergic sputum by its color alone. Sputum color change to green or yellow is a result of an enzyme (myeloperoxidase) in association with cellular breakdown during stasis. The yellow-green color, therefore, tends to signify retained or stagnant secretions. A wet-mount preparation of the sputum can be useful in differentiating between allergic and infectious problems. A wet-mount specimen is prepared by teasing a small particle of mucus from the sputum specimen and placing it on a slide. A drop of crystal violet solution may be added and a cover slip is pressed down over the preparation. The slide is then examined through a microscope to determine whether the predominant cells are neutrophils (indicative of infection) or eosinophils (indicative of allergy). A Wright stain can be used to determine the same information; however, the wet-mount preparation is quicker and can be done easily in the physician's office.

If the sputum contains predominantly neutrophils, the condition will very likely respond to an antimicrobial agent. However, if the sputum is loaded with eosinophils, administration of a corticosteroid is the treatment of choice. In an out-

patient, it seems appropriate empirically to start antimicrobial therapy if the patient's sputum increases in amount, becomes thicker or turns yellow-green. However, if there is no satisfactory response in 48 to 72 hours, a sputum wet-mount examination is indicated. The patient may have a respiratory infection and the antimicrobial agent selected may not have affected the causative organism. It can also be determined if the increased sputum difficulty is not related to an infection but, in fact, is a manifestation of allergy.

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REFERENCES

Chodosh S: Examination of sputum cells. N Engl J Med 282: 854-857, Apr 9, 1970

Epstein RL: Constituents of sputum: A simple method. Ann Intern Med 77:259-265, Aug 1972

Weaning Criteria for Patients on Mechanical Respiratory Assistance

IN ORDER to understand the criteria that commonly are used to determine whether patients are ready for weaning from mechanical ventilation, it is necessary to review some of the physiologic changes that may occur in those who are successfully weaned. During the first day off a ventilator there is usually a 50 percent rise in vital capacity, the tidal volume increases by about 1 ml per kg of body weight and the patient's spontaneous maximum inspiratory force increases by 6 cm of water. There is little change in the lung compliance, functional residual capacity or dead space-to-tidal volume ratio (V_D/V_T). Invariably, there is a transient rise in the arterial carbon dioxide pressure. A small rapidly developing increase in right-to-left shunt occurs, which is reflected in a widening of the alveolar-to-arterial oxygen tension difference (A-a D_{O_2}). In some patients there is a rise in the cardiac output; in others it falls. Significant changes in pulse and blood pressure are rarely seen. Most patients also experience some degree of sympatho-adrenal stimulation.

Many of the commonly used criteria are good predictors of successful weaning because they reflect the magnitude of these physiologic changes. The patient's underlying disease, which led to respiratory failure and mechanical ventilatory support, influences which criteria may be helpful in predicting that the time for weaning has arrived.

In general, the criteria for discontinuance are the reverse of the criteria for beginning mechanical ventilatory assistance. In patients with neuromuscular disease, a vital capacity of at least 10 ml per kg of body weight, or in adults at least 1.0 liter, and a maximum inspiratory force of at least −20 cm of water are desirable. In the acute hypoxic states—such as noncardiogenic pulmonary edema, aspiration pneumonia or fat embolism—a system compliance of at least 30 ml per cm of water, and $\Delta A\text{-}a_{o_2}$ of less than 200 mm of mercury (fraction of inspired oxygen, 1.0) or an arterial oxygen pressure-to-fraction of inspired oxygen ratio of at least 200 are desirable. In patients with obstructive airways the fraction of inspired oxygen, a spontaneous minute ventilation of less than 10 liters per minute, which can be doubled with effort, and a maximum inspiratory force of at least −20 cm of water probably indicate that weaning can commence. During spontaneous breathing the arterial carbon dioxide pressure should not rise faster than 2.0 mm of mercury per minute. In most instances of respiratory failure, the recovering V_D/V_T should usually be less than 0.6. Observation of vital signs after discontinuance of mechanical assistance is also important. The heart rate should not exceed about 120 per minute and the mean arterial blood pressure should not rise by more than 15 mm of mercury. No worsening of cardiac arrythmia should occur. Greatly increased metabolic rates, as seen in patients with high fever, or abnormalities of electrolytes may also make weaning difficult.

It should be stressed that none of these criteria are absolute predictors. It is not easy to accurately assess diaphragm function, metabolic work and cardiac function at the bedside. Therefore, these criteria are guidelines. They should alert a physician to the likelihood of success or failure in weaning a patient but they should not necessarily deter initiating an attempt to restore patient support of respiration.

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REFERENCES

Hedley-Whyte J, Burgess GE, Feeley TW, et al: Applied Physiology of Respiratory Care—Criteria of Weaning. Boston, Little, Brown Co., 1976, pp 136-138

Hodgkin JE, Bowser MA, Burton GG: Variation in the occurrence of extracellular diffusible antigens in temperature-induced variants of Erwinia herbicola Y46, and observations of their relationships with Erwinia amylovora. Crit Care Med 2:96-102, Mar-Apr 1974

Skillman JJ, Malhotra IV, Pallotta JA, et al: Determinants of weaning from controlled ventilation. Surg Forum 22:198-200, 1971

Biofeedback in Pulmonary Diseases

DYSPNEA, carbon dioxide retention and persistent dry cough are problems in pulmonary management particularly suited to ancillary therapy with biofeedback. In each instance, patients' own instinctive adaptive responses—work harder to breathe, breathe faster and really try to force out the irritant—only serve to aggravate and perpetu-

ate the problem. To gain lasting improvement, patients' maladaptive behavior must be corrected; such is not possible by pharmacologic means alone. The patient must be shown what he is doing incorrectly, and the change necessary to gain the desired benefits. This training must be conducted on a regular repetitive basis with expert coaching appropriate to the occasion.

To keep costs down and availability high we rely mainly upon standard hospital equipment. The "workhorse" is the spirometer with carbon dioxide absorber and recirculating fan and enough extra oxygen to last 15 minutes. The patient is positioned so that he can see his own tracing and a base line obtained. While watching his tracing, he is urged to change his performance in the desired direction. We also employ galvanic skin resistance meters for tension reduction and electromyogram equipment for muscle education in parallel sessions. Peak flow meters and self auscultation are used to teach early detection of bronchospasm and more effective assumption of preventive measures. Since respiratory control is a varying amalgam of voluntary and autonomic control, we show the overpressures generated during coughing and subsequent reduction in flow rates to the patient. He is shown how to phonate continuously during cough, to prevent this overpressure. We follow with use of a 3 cm (water pressure) expiratory valve to slow respirations, increase tidal volumes and promote opening of collapsed airways. Early identification of the *anti-therapy* patient, who will require an entirely different approach, is an additional derivative of this methodology.

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REFERENCES

Segal J: Biofeedback as a medical treatment. JAMA 232:179-180, Apr 14, 1975

Vachon L, Rich ES, Jr: Visceral learning in asthma. Psychosom Med 38:122-130, Mar-Apr 1976

Value of Lung Scanning in Evaluating the Risk of Thoractomy

EQUAL IN IMPORTANCE to determining whether a lung lesion is resectable is whether or not the patient can survive the operation. To completely resect a malignant lesion of the lung but have the patient die in respiratory failure in the immediate postoperative period or be left a severe respiratory cripple is not acceptable.

A patient's ability to tolerate removal of a lung has been evaluated by such techniques as having the patient walk down the corridor with the physician, walk up stairs, or blow out a match. Recognizing that these are only rough guides to a patient's total respiratory function, more sophisticated methods for determining how much lung function would remain following a resection were developed. These included bronchospirometry and the determination of pulmonary artery pressure after occlusion of the pulmonary artery to the lung to be resected. Recently, it was shown that selective lung function can be determined *noninvasively* and relatively simply with the use of radioisotope lung scanning.

With the use of xenon 133 or technetium 99m, quantitative perfusion lung scans can be done which allow for estimates of the expected loss of function that would result from the anticipated resection of lung tissue. For example, the postoperative forced expiratory volume in one second (FEV_1) is predicted by multiplying the preoperative FEV_1 by the fraction of function that is found in the lung that is to remain after resection. Elective resection is inadvisable if the predicted postoperative FEV_1 is less than 0.8 liters, particularly without further studies such as balloon occlusion of the pulmonary artery to the lung to be resected.

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REFERENCES

Olsen GN, Block AJ, Tobias JA: Prediction of postpneumonectomy pulmonary function using quantitative macroaggregate lung scanning. Chest 66:13-16, Jul 1974

Boysen PG, Block AJ, Olsen GN, et al: Prospective evaluation for pneumonectomy using the 99m technetium quantitative perfusion lung scan. Chest 72:422-425, Oct 1977

Hodgkin JE: Evaluation before thoracotomy. West J Med 122:104-109, Feb 1975

Evaluation of Small Airways Function

SMALL AIRWAYS of 2 mm in diameter or less constitute the largest total volume of conducting airways in the lung yet direct measurement of these structures is not yet routinely possible. However, several simple and not so simple tests are available which give good indirect evidence of a critical portion of the lung that Dr. Jere Mead of Harvard has called the "silent zone." It has long been appreciated by clinicians that malfunction leading to obstruction of airflow begins and progresses significantly before development of symptoms or abnormalities on conventional spirometry. A general nihilism toward pulmonary testing developed among clinicians over the years because tardiness of diagnosis led to advanced disease unresponsive to therapy, even when acted upon promptly after diagnosis.

When usual spirometric values show airways obstruction, the search for small airways disease (SAD) is redundant, even wasteful. Detection of SAD is the prerequisite to early detection of re-

versible airways disease. The tests used to detect SAD fall into three categories: (1) measures of airflow due to airways resistance, (2) measures of distribution of gases in the lung and (3) measures of airflow due to the elastic properties of the lung. Frequency dependence of dynamic compliance, a combination of categories 1 and 3, is considered the most specific and is often used to correlate with newer tests; however, it is technically difficult and requires placement of an esophageal balloon.

The standard spirogram measures volume against time, from which many defined flows are determined, the most popular being the forced expiratory volume in one second (FEV_1). The same maneuver can be viewed as flow against volume, the maximum expiratory flow volume (MEFV), from which is calculated the vital capacity (VC), the peak flow (PF) and instantaneous flows when 75 percent (V75), 50 percent (V50) and 25 percent (V25) of the VC remains to be exhaled. The V50 and the V25 have been shown to be the most specific indicators of SAD, as has the appearance of concavity of the tracing from PF to residual volume (RV). The best measure of this concavity is the V50 measure, but the V25 is most effort independent and reflects more the flow through smaller airways. The MEFV can be done with the patient breathing air or a helium-oxygen mixture. When the two curves are superimposed, the volume at which the flows become identical increases as SAD develops. This *isoflow* volume is usually near the V25 flow but approaches the V50 flow with disease.

A recent reevaluation of the single-breath nitrogen test led to its use as in screening for SAD. The important components of the test are called closing volume, closing capacity, and ΔN_2 or slope of phase III. Recent criticisms of the test as being too nonspecific were set aside by Cosio and co-workers, who recently correlated function with pathology in living subjects. SAD lesions could best be reliably detected ($P<0.05$) using three tests: (1) closing capacity, (2) volume at isoflow, the volume at which air and helium flow were equal (a test of airway caliber and elastic recoil) and (3) the slope of phase III of the single-breath washout (a test of evenness of distribution of ventilation). These tests correlate with potentially reversible pathologic changes, are noninvasive and are simple to carry out. Much less sensitive are certain measures of the spirogram (such as maximum mid-expiratory flow and FEV_1). Reductions in the FEV_1 and the $FEV_{1.0}/FVC$ ratio are "late" findings; therefore, one must conclude that apparently small changes in the standard spirogram represent significantly advanced disease. Decrements in the spirogram with time are significant, and repetitive measures at annual or semiannual intervals may be useful for risk subjects. Azen and associates compared smokers and nonsmokers using the tests mentioned above. They found the ΔN_2 to most significantly differentiate smokers from nonsmokers, and showed a trend toward dysfunction in all smokers and reversal of dysfunction in exsmokers. Tests of SAD are not used to uncover the obvious; it is easier to ask than test if a patient smokes. SAD can be uncovered in populations easily, and are useful in individual risk assessment and effective patient intervention.

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REFERENCES

Cosio M, Ghezzo H, Hogg JC, et al: The relations between structural changes in small airways and pulmonary-function tests. N Engl J Med 298:1227-1281, Jun 8, 1978

Azen SP, Linn WS, Hackney JE, et al: A comparison of eight lung function indices in smoking and nonsmoking office workers. Lung 154:213-221, 1977

Macklem PT: Obstruction in small airways—A challenge to medicine. Am J Med 52:721-724, Jun 1972

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EDITORIALS

Some Conceptual and Practical Problems Facing Medicine

A GENERATION or so ago the trusted and beloved family doctor became largely superseded by the present-day scientific medical specialist. The faith that had been placed in the family doctor was transferred to modern medical science with great patient and public expectations for it. When this highly touted and very much oversold medical science did not fulfill these expectations, this faith was shaken, and there has been considerable disillusionment which has been largely focused on the medical profession. The ramifications of this disillusionment have been many and far-reaching, and among other things have given rise to a number of fundamental conceptual and practical problems which now face medicine. Many of these seem to require some sort of practical blending of conceptual opposites.

• For example, it is no longer accepted by the public that physicians and the medical profession will protect the interest of patients and the public without more safeguards. Professional peer review alone does not satisfy the public interest or concern. Yet persons outside the profession are often incapable, or at least at great disadvantage, when they attempt to pass judgment on medical matters for which they have no professional training or experience. Professional responsibility and public accountability are in a sense conceptual opposites which are now giving rise to practical problems.

• The public, through government, has encouraged both the production of more physicians and the proliferation of so-called second level practitioners both in numbers and scope of practice. It seems likely that there will soon be too many practitioners in the health field; that is, more than can be supported. If there is to be a surfeit of health care practitioners, the capabilities, limitations and turf of each will need to be defined, and the essential and distinctive roles of doctors of medicine identified and recognized. There is much to be worked out here at both conceptual and practical levels.

• Medical science is the mast to which we have nailed our professional flag, yet if we were asked never to use any procedures or treatments that had not been scientifically proven or verified, we would be in a sad situation. Medicine is an art as well as a science, and patients have benefitted from the art far longer than they have from the science. There are many conceptual and practical problems to be dealt with as the cost effectiveness of what physicians do becomes increasingly questioned by a nonprofessional and cost conscious public.

• Caring was the forte of old-time family doctors. They could do little curing. Curing is the forte of modern scientific physician practitioners. As specialized curing has moved into the ascendancy in medical education and patient care it has often been at the expense of attending the whole patient—and of caring. The present tendency to polarize these functions into scientific medicine on the one hand and holistic health on the other is producing unwanted schisms in patient care. There are conceptual and practical problems to be resolved here, but the tent of medicine must always have room for genuine curing and genuine caring for the whole person by whatever means these can be accomplished.

• During the last few years there have been significant attempts by government to force medical care into the mold of a trade in the hope that, by reducing restraints on trade, costs would be decreased. An opposite force, a desire to assure quality, is also at work. This has been a specific goal of the medical profession in the United States since 1910, and the profession has developed systems of accreditation, certification and fee studies to accomplish it. Here again are conceptual opposites, giving rise to very practical problems.

These are only some examples of the kind of fundamental problems that confront the medical profession today. One senses that we have no

really effective means in organized medicine to study them in any sort of depth, or to develop realistic policies that will recognize the need to find an accommodation between such conceptual opposites which impinge upon physicians and patient care. It is unlikely that problems such as these can be solved by medicine alone, but neither can they be solved without medicine's leadership and the support of public opinion. It is not too early for the medical profession, through its leadership, to begin to think through some of these conceptual issues and then, perhaps in concert with others, to develop policies to deal more effectively with some of the practical problems that are even now at hand.

—MSMW

Mount Olympus Revisited

To the ancient Greeks, Mount Olympus was the abode of the gods, and any mortal venturing there did so at his peril. Although our appreciation of the hazards of mountainous regions has changed over the centuries, respect and caution are still advisable. Not only are the terrain and weather often hostile, but there are the added hazards posed by the inescapable hypoxia resulting from the lower atmospheric pressure at high altitude. Elsewhere in this issue, Hultgren has dealt with these hazards in his excellent review of high altitude medical problems. Very properly, the reader is confronted with the reality that life-threatening altitude sickness can develop at elevations no higher than 9,000 feet, and that millions of Americans enter this danger zone each year when they visit our Western mountains. Altitude sickness is not a medical curiosity encountered only by foolhardy climbers at extreme altitudes in remote corners of the world. It is a potential threat to average tourists on vacation in the Rockies or the Sierras. Fortunately, the incidence of serious problems is low, but physicians must be aware of the problems that may arise.

A persons driving into the mountains is exposed to a progressively lower atmospheric pressure. Although the concentration of oxygen remains constant at 21 percent, the partial pressure of oxygen falls as the total atmospheric pressure decreases. It is this atmospheric hypoxia that disturbs the mechanisms of oxygen transport in the body, and initiates the normal processes of adaptation. During this transition from normoxia to hypoxia, acute mountain sickness (AMS) appears. No underlying disease process is involved. However, the exact pathogenesis of AMS is poorly understood, and the basis for individual variability is unknown. Hence, the physician's approach must be that AMS may develop in anyone, and the likelihood is enhanced the greater and more rapid the change in altitude—that is, the greater and more abrupt the hypoxic stimulus. As Hultgren emphasizes, the most effective way to avoid AMS, therefore, is to make the ascent gradual.

Americans always seem to be in a hurry, and many will simply not heed the advice of gradual ascent. They will fly to Denver (5,300 feet), rent a car and in a matter of hours be at a mountain resort area such as Keystone (located at 9,300 feet elevation). Predictably, half of these people will suffer some degree of AMS.[1] While more gradual ascent will reduce the incidence of AMS, in some persons symptoms will still develop. Realistically, then, a certain amount of AMS is inevitable. Fortunately, most cases of AMS are self-limiting. However, it is those persons with AMS whose conditions progressively deteriorate who are at serious risk. We must educate the public in recognizing this latter situation.

Hultgren presents definitive descriptions of the various forms of AMS, including high altitude pulmonary edema (HAPE) and cerebral edema. These are based on his long-standing interest, his research and his extensive firsthand experience treating patients with AMS both in the Sierras and in the Andes. There is uniform agreement that the most reliable form of treatment of AMS is prompt descent. Furthermore, descent should be initiated at the first indication that the person's condition is deteriorating rather than showing the usual spontaneous improvement. To wait and see if the person's condition will get worse can convert an ambulatory patient to one who must be carried, and such delays have proved fatal. Since the initiating cause of AMS is atmospheric hypoxia, the ultimate goal of therapy is relief of hypoxia. Hence, supplemental oxygen is useful. However, Hackett, Rennie and Levine have reported that in treating patients with AMS at 14,000 feet, descent to 11,000 feet produced dramatic improvement whereas supplemental oxygen at the higher altitude did not.[2]

Paradoxically, high altitude natives are not immune to AMS, as Hultgren points out. In fact, such natives may have an exaggerated suscepti-

bility to HAPE after a sojourn at low altitude as brief as one or two days.[3] Some aspect of their long-term acclimatizations appears to be lost rapidly, rendering them vulnerable upon reascent to their home environment. It is true, as Marticorena and Hultgren[4] have reported recently, that high altitude natives in whom HAPE develops upon reascent can be treated effectively while remaining at high altitude with oxygen and rest, or perhaps even bed rest alone. However, such high altitude natives differ physiologically from unadapted lowlanders. I have observed trekkers with HAPE at 14,000 feet whose conditions did not improve with rest and supplemental oxygen for 48 hours, and in whom improvement occurred only when helicopter evacuation became available. Consequently, we should be cautious in extrapolating experience gained from high altitude natives when confronted with a lowlander with AMS. Prompt descent remains the most reliable form of treatment, and prevention the ultimate goal.

With ever-increasing numbers of visitors to the high altitude regions of the world, the medical problems of high altitudes will become more frequent and more familiar. We must consider not only those millions seeking recreation in the mountains, but also those persons who are taking up residence at high altitude for such industrial purposes as oil shale development, mining of molybdenum above 12,000 feet and construction of the Eisenhower tunnel at 11,300 feet under Loveland Pass in Colorado, as well as the families of such workers who populate communities like Leadville, Colorado, at 10,200 feet. From pregnant women to infants to the elderly with poor health, long-term residence at high altitude poses another set of medical problems which we are only beginning to appreciate, much less understand. The review by Hultgren in this issue is indeed timely.

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REFERENCES

1. Anholm JD, Houston CS, Hyers TM: The relationship between acute mountain sickness and pulmonary ventilation at 2,835 meters (9,300 ft.). Chest 75:33-36, 1979

2. Hackett PH, Rennie D, Levine HD: The incidence, importance, and prophylaxis of acute mountain sickness. Lancet 2: 1149-1154, 1976

3. Scoggin CH, Hyers TM, Reeves JT, et al: High altitude pulmonary edema in the children and young adults of Leadville, Colorado. N Engl J Med 297:1269-1272, 1977

4. Marticorena E, Hultgren HN: Evaluation of therapeutic methods in high altitude pulmonary edema. Am J Cardiol 43: 307-312, 1979

Lessons From Skull Films

THE BRIEF REPORT "Skull Radiography and Professional Liability" which appears elsewhere in this issue has obvious lessons which illustrate its title. A skull film reported as normal may not be, or it may be apparently normal but fail to disclose a significant abnormality that actually is present—with all the risks that this implies for both patient and physician. This is evident enough. But there are other lessons to be extracted from this simple report. For example, a less expensive procedure, such as making a roentgenogram of the skull, may not be as cost-effective as one that is more expensive, such as computerized tomography. This fact may make the use of less costly and less effective procedures unnecessary, or prevent delays in diagnosis which may in turn add, perhaps tragically, to the disability and the cost. In the cost conscious times we are in, there is need for more attention to actual cost benefits, as more sophisticated and more expensive techniques become available to practicing physicians. And another lesson is that perhaps it is time to review and update our thought processes in patient care, to question some of the stereotypes of practice (a skull film will reassure the patient and provide some legal protection for the physician) and to reexamine what we are doing and why we are doing it—particularly when science and technology make available new, though perhaps more expensive, approaches to medical care.

—MSMW

Implications of Successful Combination Chemotherapy for Testicular Germ Cell Neoplasms

ELSEWHERE IN THIS ISSUE Einhorn and Williams outline their chemotherapy results for recurrent and metastatic testicular germ cell neoplasms. Results of their trials[1] as well as those of others[2] have significantly altered the prognosis of patients with such tumors. It is important to place these advances in perspective and examine their implications in terms of the overall approach to germ cell neoplasms.

The historical development of combination chemotherapy for testicular tumors can be seen as consisting of three significant steps. The *first generation* of combination chemotherapy was introduced by Li and co-workers[3] when they reported the first successful combination chemotherapy of testicular cancer in 1960 in which seven of 23 patients treated with an alkylating agent (chlorambucil), the antibiotic dactinomycin and the antimetabolite methotrexate had what could now be considered a complete response. Three of the original seven patients are apparently still alive and free of disease 20 years later. Over the next decade a number of investigators using similar regimens produced approximately 5 percent to 15 percent complete response rates; the regimens were by current standards minimally toxic.[2] The *second generation* of chemotherapy was ushered in by Samuel and associates when they reported their data on the combination of vinblastine and bleomycin.[4] This regimen was more toxic than the earlier regimens which were based on alkylating agents, but produced a 39 percent complete response rate and in good risk, previously untreated patients produced equal to or greater than 50 percent complete responses. The *current generation* combination chemotherapy expands upon the work of Samuel and his colleagues by the addition of Cis-dichlorodiammine platinum II, perhaps the most active chemotherapeutic drug for testicular neoplasms. The regimen of Einhorn and associates,[1] the regimens used at Memorial Sloan Kettering (VAB III, VAB IV) and at Roswell Park Memorial Institute consistently produce 50 percent to 75 percent complete response rates.[2] Relapse rates of the most modern regimens are equal to or less than 25 percent, thus approximately 50 percent of all patients with advanced disease are alive and free of disease from months to years. While the follow-up time of most modern chemotherapeutic regimens is a matter of only a few years, the fact that most patients who will relapse after chemotherapy do so in the first 12 to 15 months suggests the possibility that many of these young men may indeed be cured.

Careful analysis of response rates and relapse patterns provides insight into new chemotherapeutic approaches currently being evaluated and indicate that a reappraisal should be made of the approach to earlier stage disease. In every series reported, the efficacy of modern combination chemotherapy is remarkable if the patient being treated has a minimal tumor burden (that is, equal to or greater than 80 percent complete response rate) while the same regimen produces equal to or less than a 50 percent complete response rate if the patient has a large tumor burden with advanced retroperitoneal nodes or large pulmonary metastasis; the prognosis is particularly bad if metastatic lesions are present in organs other than the lung. Current trials are underway to test modification of therapy for these different subgroups of patients with vastly different prognoses. Einhorn has initiated a study to determine whether maintenance chemotherapy, common to most current protocols, is in fact needed. Furthermore, because of the significant morbidity of his original regimen due to bone marrow suppression, he is testing a new regimen with a lower dose of vinblastine to determine whether one can achieve comparable response rates with less toxicity. As alluded to in his article, this regimen is probably adequate at least for the good prognosis patient with minimal tumor burden. In contrast, new innovative approaches must be utilized for the poor risk patient with a large volume of tumor in whom the complete response rate is equal to or less than 50 percent. One approach is to incorporate cytoreductive surgical therapy with the chemotherapy; several institutions have begun such studies. Another approach would be to escalate the chemotherapy to levels which produce bone marrow ablation—such an approach would require a protected environment (laminar flow rooms) or autologous bone marrow transplantations, or both—highly experimental but clearly justified for this young patient population with a particularly bad prognosis.

Finally, the efficacy of combination chemotherapy forces one to reevaluate the therapy of stage I and stage II testicular carcinoma. A retroperitoneal lymph node dissection has been considered the standard approach for these patients, combining a staging and therapeutic tool. Stage I patients whose lymphadenectomy is negative have an excellent prognosis with greater than an 80 percent cure rate (the lymphadenectomy obviously in retrospect was only of staging import but was not therapeutic in this patient population). The cure rate for stage II disease, where retroperitoneal nodal metastases are identified, varies from 30 percent to 70 percent depending upon the series reported. The pronounced disparity in cure rate relates to the inadequacy of the earlier staging system since the stage II designation spans the

gamut of patients with one positive retroperitoneal node to patients with massive unresectable disease encroaching upon ureters, great vessels, and so forth. (Application of the newer staging system which subdivides stage II disease in four subgroups based upon the extent of retroperitoneal involvement will allow for more accurate evaluation of therapeutic trials.[2]) In other countries, radiotherapy is utilized for testicular cancer as well as for testicular seminomas. Long-term disease-free rates are reported which are comparable to the surgical series both in stage I and stage II disease.[2] Since radiotherapy does not produce a dry ejaculate as may occur after lymphadenectomy, it would be desirable to compare these two modalities of therapy. However, the ability to effectively treat patients with chemotherapy may be compromised by the bone marrow suppression produced by radiotherapy, so it is important that such a study be a carefully designed, strictly controlled clinical trial. However, because of the rarity of this disease process and the vested interest (ego, status, financial remuneration) of the specialties involved, it is unlikely that such a trial will ever be easily performed.

In context with the above reevaluation, the question of adjuvant combination chemotherapy for stage I and stage II disease must also be addressed. The data on efficacy of combination chemotherapy in patients with small tumor burdens suggest that adjuvant chemotherapy should be maximally effective in such an adjuvant setting, and a nationwide intergroup study has been initiated to address this question. This is of major significance since the chemotherapy should be notably effective, but also carries known immediate risks and as yet unknown long-term risks in a patient population whose life expectancy may be equal to or greater than 50 years after surgical operation (or radiotherapy). The experience in the therapy of Hodgkin disease raises the possibility of permanent sterility or a higher risk of a second malignancy, or both.[5] As Einhorn points out, the chemotherapy may be so efficacious that most patients may be cured if their relapse after surgery (or radiotherapy) is recognized early with very careful follow-up utilizing lymphangiograms, computerized tomography, ultrasonography and, most important, the highly sensitive and specific tumor markers, alpha fetoprotein and human chorionic gonadotropin. Such an approach would spare a significant number of patients the morbidity of chemotherapy unless the necessity of such therapy is documented by the demonstration of recurrent disease.

The next decade will witness the refinement in the therapy for patients with testicular cancer. While caution must be exercised to avoid overinterpretation of results, and is predicated upon the assumption that a few years' experience translates into a lifetime prognosis, the outlook for patients with carcinoma of the testis has dramatically improved. We are on the threshold of developing a coordinated therapeutic approach which will produce potential cure for most patients with testicular germ cell neoplasms.

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REFERENCES

1. Einhorn LH, Donohue J: Cis-diamminedichloroplatinum, vinblastine and bleomycin combination chemotherapy in disseminated testicular cancer. Ann Intern Med 87:293-298, 1977

2. Anderson T, Waldmann TA, Javadpour N, et al: Testicular germ cell neoplasms: Recent advances in diagnosis and therapy. Ann Intern Med 90:373-385, 1979

3. Li MC, Whitmore WF, Golbey R, et al: Effects of combined drug therapy on metastatic cancer of the testis. JAMA 174:1291-1299, 1960

4. Samuels ML, Johnson DE, Holoye PY: Continuous intravenous bleomycin (NSC125066) therapy with vinblastine (NSC-49842) in Stage III testicular neoplasia. Cancer Chemotherapy Reports 59:563-570, 1975

5. Arseneau JC, Canellos GP, DeVita VT Jr, et al: Recently recognized complications of cancer chemotherapy. Ann NY Acad Sci 230:481-488, 1974

CASE REPORTS

Refer to: Samuelson CO JR, Williams HJ: Ibuprofen-associated aseptic meningitis in systemic lupus erythematosus. West J Med 131:57-59, Jul 1979

Ibuprofen-Associated Aseptic Meningitis in Systemic Lupus Erythematosus

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IBUPROFEN (Motrin), a nonsteroidal anti-inflammatory drug of the propionic acid group, is now frequently used in inflammatory musculoskeletal disorders, including systemic lupus erythematosus (SLE). Central nervous manifestations in SLE are highly variable and frequently present problems in diagnosis and management. Recently Widener and Littman[1,2] reported three cases in which ibuprofen may have contributed to aseptic meningitis in SLE. Wasner[3] has also suggested this association in one case. Here we report an additional case in which fever, myalgia, headache and mental confusion were temporally related to ibuprofen ingestion.

Report of a Case

A 21-year-old single white woman visited her physician in October 1974, with complaint of fatigue, fever and multiple pains in the joints. The patient's erythrocyte sedimentation rate (ESR) was 44 mm per hour, antinuclear antibody studies and lupus erythematosus cell preparation were positive, and findings from other studies showed no abnormalities. Aspirin was prescribed but discontinued as a result of tinnitus and gastrointestinal irritation. Ibuprofen therapy, 300 mg four times a day, was begun but was also discontinued because of gastrointestinal irritation, headache, and exacerbation of arthralgia and fever. The patient's condition then gradually improved until six months later when she was first seen in the Arthritis Clinic, University of Utah Medical Center; complaints included a temperature of up to 40°C (104°F); pain in the fingers, wrists and knees; increased fatigability, and a photosensitive skin rash. Physical examination showed no abnormalities except for swelling, heat and tenderness in the wrists, metacarpal phalangeal and proximal interphalangeal joints. No rash, alopecia, Raynaud phenomenon, pleuritis, pericarditis or neurologic abnormalities were present. Findings on a hemogram and on analysis of urine were within normal limits, the ESR was only slightly elevated at 27 mm per hour by the Westergren method, antinuclear antibody studies were positive and a rheumatoid latex fixation test was negative. Serum C3 and C4 were within normal limits. The previous diagnosis of systemic lupus erythematosus was supported by these results and the patient was treated with aspirin, 650 mg four times a day. Approximately one month later, increasing pain in the joints and stiffness and swelling of the left knee occurred. An erythematous rash appeared on the face and body and therapy with hydroxychloroquine sulfate was started, 200 mg twice a day. The patient's symptoms were progressive and prednisone therapy, 5 mg per day, was started in May 1975, with improvement in symptoms. Prednisone therapy was stopped in August 1975 and, except for mild arthritis, symptoms resolved.

On February 12, 1976, increasing fatigue developed, along with painful swelling of the patient's feet, knees, fingers and wrists. The patient said that fever, rash, headache or other symptoms had not occurred. Results of examination showed an effusion in the left knee and tenderness with painful motion of the shoulders and right knee. Analysis of urine showed no abnormalities, hematocrit was 41 percent, leukocyte count was 5,200 per cu mm with normal differential, and the ESR was 31 mm per hour. Ibuprofen, 400 mg four times a day, was prescribed, and on February 13, 1976, the patient was admitted to the University of Utah hospital after several hours of fever, headache, nausea and vomiting, which began

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shortly after administration of ibuprofen. The patient's temperature was 37.7°C (100°F), pulse rate was 100 and blood pressure was normal. Examination of the joints showed no changes, but there was a painful stiffness in the neck with no localized neurological findings. A lumbar puncture was done and analysis of the cerebrospinal fluid showed 50 nucleated cells per cu mm, of which 21 were polymorphonuclear neutrophils; the glucose value was 43 mg per dl (serum glucose, 114 mg per dl) and the protein level was 59 mg per dl. The Gram stain and India ink preparation were negative. While cultures were being done, therapy with penicillin G, 2 million units given intravenously every four hours, was started and ibuprofen therapy was stopped. Four days later, findings from a second lumbar puncture showed 15 mononuclear cells per cu mm and normal protein and glucose levels. Counterimmune electrophoresis was negative for pneumococcal, meningococcal and hemophilus influenza type B antigens. The cultures remained negative and the findings seemed consistent with aseptic meningitis. Administration of antibiotics was discontinued. The patient's condition improved and she was discharged, on a regimen of aspirin and hydroxychloroquine sulfate.

She was seen one week later in clinic and physical examination showed no abnormalities except arthritis; as a result, ibuprofen was prescribed again but was not taken by the patient until February 24, 1978. Headache, nausea, and vomiting developed within hours and the patient was taken to the emergency room at the University of Utah Medical Center. On examination she had a temperature of 38.1°C (100.6°F) but vital signs and nuchal rigidity were normal. Neurological examination showed no localizing signs but the patient was moderately obtunded. Results of a lumbar puncture showed 3,300 nucleated cells per cu mm with 99 percent polymorphonuclear neutrophils. Gram stain and counterimmune electrophoresis for pneumococcal, meningococcal and hemophilus influenza type B antigens were negative. The cerebrospinal fluid glucose value was 10 mg per dl (serum glucose, 152 mg per dl). A probable diagnosis of bacterial meningitis was made and therapy with high doses of penicillin, given intravenously, was started. The obtundation gradually cleared and the cerebrospinal fluid returned to normal in one week. All cultures were negative. Results from a computed tomography scan were also normal. The question of ibuprofen toxicity was raised because of the temporal relationship of the drug to exacerbations, and appropriate warnings were given. The patient has had no further neurological manifestations in 30 months of follow-up without ibuprofen therapy. The SLE has remained reasonably controlled although she has had recurrent pleuropericardial effusions responsive to aspiration and various increases in oral steroids.

Comment

While central nervous system disturbances are clearly seen in SLE, a presentation consistent with aseptic meningitis is rare.[4,5] Because the diagnosis of aseptic meningitis and central nervous system manifestations of SLE are both made largely on exclusionary grounds, precise diagnosis is difficult. There is evidence that ibuprofen may have been associated with aseptic meningitis in patients with SLE.[1-3] Another case has been reported with similar findings and at least one temporally related challenge with ibuprofen therapy, again resulting in an episode of aseptic meningitis.

Aseptic meningitis induced by drugs other than ibuprofen has been reported,[6-8] but, as in this case, the mechanism of action is not known. The rapid onset of symptoms after the ingestion of ibuprofen in this patient could be a result of a drug-hypersensitivity reaction or direct irritation. Ibuprofen inhibits prostaglandin synthesis,[9] but it is doubtful that this caused aseptic meningitis in this patient. Aspirin, also an inhibitor of prostaglandin synthesis,[9] was ingested by the patient without evidence of the symptoms seen after ibuprofen therapy. It is interesting that drugs of this class have also been shown to decrease renal function in patients with SLE.[10]

Ibuprofen and other chemically related drugs are now commonly used for multiple rheumatic problems, but the aseptic meningitis syndrome has been reported only in patients with SLE who are treated with ibuprofen. While this may represent a unique linkage of drug properties and patient sensitivity, the development of new or changing neurological signs in patients receiving phenylalkanoic acid derivatives warrants careful observation and perhaps reassessment of the therapeutic regimen.

Summary

Ibuprofen is now frequently used in disorders involving inflammatory connective tissue, including systemic lupus erythematosus. Although asep-

tic meningitis is unusual in patients with systemic lupus erythematosus, recently it has been suggested that aseptic meningitis may be induced by the administration of ibuprofen. We report a case in which aseptic meningitis developed in a patient treated with ibuprofen for systemic lupus erythematosus.

REFERENCES

1. Widner HL, Littman BH: Ibuprofen induced lymphokine production and meningitis in systemic lupus erythematosus. Presented at XIV International Congress of Rheumatology, Jun 28, 1977 (Abstract 809)

2. Widener HL, Littman BH: Ibuprofen-induced meningitis in systemic lupus erythematosus. JAMA 329:1062-1064, 1978

3. Wasner CK: Ibuprofen meningitis and systemic lupus erythematosus. Rheumatol 5:162-164, 1978

4. Johnson RT, Richardson EP: The neurological manifestations of systemic lupus erythematosus. Medicine 47:337-369, 1969

5. Canoso JJ, Cohen AS: Aseptic meningitis in systemic lupus erythematosus. Arthritis Rheum 235:369-374, 1975

6. Farmer L, Echlin FA, Loughlin WC, et al: Pachymeningitis apparently due to penicillin hypersensitivity. Ann Intern Med 52:910-914, 1960

7. Garagusi VF, Neefe LI, Mann O: Acute meningoencephalitis: Association with isoniazid administration. JAMA 235:1141-1142, 1976

8. Barrett PVD, Thier SO: Meningitis and pancreatitis associated with sulfamethizole. N Engl J Med 268:36-37, 1963

9. Flower RJ: Drugs which inhibit prostaglandin synthesis. Pharmacol Rev 36:33, 1974

10. Kimberly RP, Bowden RE, Keiser HR, et al: Reduction of renal function by newer nonsteroidal anti-inflammatory drugs. Am J Med 64:804-807, 1978

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Clonidine Hydrochloride Withdrawal Complicating Bilateral Nephrectomy

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CLONIDINE HYDROCHLORIDE is an effective antihypertensive agent that has been used in the management of moderate to severe hypertension.[1-5] The presumed site of action is at the level of the brain stem where the drug has a stimulatory effect on a vasomotor inhibitory pathway. Activation of this pathway reduces sympathetic vasomotor tone at the periphery and decreases systemic blood pressure.[6-9] Clonidine hydrochloride has also been shown to decrease the secretion of renin.[10,11]

The abrupt cessation of clonidine administration has been reported to cause a syndrome of sympathetic overactivity (Figure 1). Manifestations associated with this syndrome include severe hypertension, tachycardia, headache, anxiety, nausea, vomiting, and an elevation in serum and urinary catecholamines.[12,14]

Renovascular hypertension has been characterized by some authors as resulting in an elevated renin profile and clonidine has been shown to be effective in lowering the blood pressure of these patients. Strauss and co-workers have suggested that there is a greater risk of the clonidine withdrawal syndrome developing in patients with renovascular hypertension.[15] They suggested that this may be due to simultaneous reactivation of the renin-angiotensin and the catecholamine-sympathetic systems. However, the former has never been documented. We recently encountered a severe episode of hypertension in a patient several hours after bilaterial nephrectomy; the patient had been receiving clonidine for several months before administration was discontinued on the day of surgical operation. This case is presented and a mechanism is proposed for clonidine hydrochloride withdrawal syndrome.

Report of a Case

A 23-year-old white man weighing 60 kg (132 pounds), with chronic renal failure and hypertension secondary to proliferation glomerulonephritis, was admitted to hospital for bilateral nephrectomy in preparation for a kidney transplant.

The preoperative course during the previous six months of dialysis had been complicated by accelerated hypertension; this was unresponsive to salt and water depletion, as manifested by a weight loss of 6 kg. Peripheral vein renin values at this time were 240 ng per ml per hour in the supine position and 245 ng per ml per hour in the upright position (normal 0.5 to 7 ng per ml

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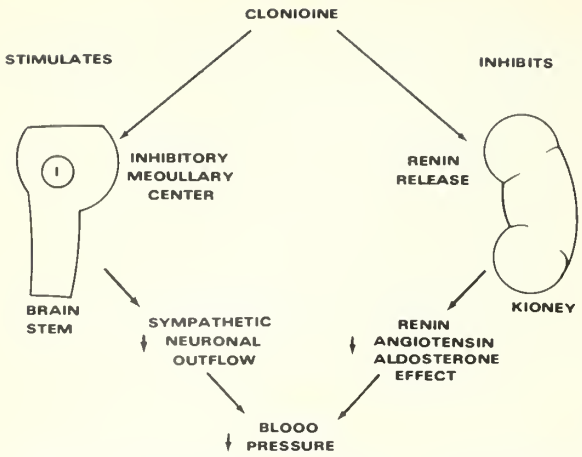

Figure 1.—Clonidine hydrochloride is proposed to stimulate an inhibitory (I) pathway in the medulla by decreasing sympathetic neuronal output and therefore reducing vasomotor tone at the periphery. It also decreases serum renin, and this may lower blood pressure. The sudden cessation of clonidine administration may leave an unopposed excitatory effect on the sympathetic neuronal outflow, which accounts for excess catecholamine levels. Also, it may be related to a rebound increase in renin.

per hour). Urine vanillylmandelic acid and metanephrines, before the onset of advanced renal failure, measured 5.9 and 0.4 mg in 24 hours (normal VMA 1.8 to 8.4 mg in 24 hours; normal metanephrines 0.3 to 0.9 mg in 24 hours). During the course of dialytic therapy the patient's blood pressure remained in the range of 190 to 200 mm of mercury systolic and 110 to 120 mm of mercury diastolic, despite varying doses of clonidine hydrochloride (1.2 to 1.6 mg per day), propranolol (720 to 960 mg per day) and minoxidil (20 to 30 mg per day). Dietary sodium during this interval was 40 mEq per day and interdialytic weight gain averaged 2 kg. One month before the patient's present admission to hospital, mild congestive heart failure developed. Because severe cardiovascular hypertensive disease was uncontrolled by medical therapy, a pretransplantation nephrectomy was scheduled.

Admission was arranged four days before surgical operation to taper the dose of antihypertensive medications. These medications included clonidine hydrochoride, 0.4 mg four times a day; propranolol, 240 mg four times a day; and minoxidil, 10 mg three times a day. The doses of minoxidil and propranolol were reduced 10 mg and 320 mg per day, respectively, and neither was given on the day of the surgical procedure. The dose of clonidine was decreased by 0.4 mg each day and 0.1 mg was given four hours before bilateral nephrectomy. To maintain blood pressure in the range of 160/90 mm of mercury, 500 mg of α-methyldopa was given intravenously every six hours.

Operative findings were limited to bilateral atrophic kidneys. Intraoperative blood pressure remained 120/80 to 130/90 mm of mercury, and there were no complications. Eight hours postoperatively, blood pressure steadily increased from between 150/70 and 160/80 mm of mercury to between 250/100 and 270/120 mm of mercury. This blood pressure rise was associated with a pulse rate of 120 to 140 beats per minute and subjective complaints of pounding in the chest and abdomen. Postoperative weight gain was 1.2 kg and peripheral pulmonary capillary wedge pressure measured 6 to 8 cm of water. Cardiac output ranged from 8 to 9.5 liters per minute, and peripheral resistance was 2,600 dynes per cubic cm.

A nitroprusside infusion, at rates of up to 400 μg per minute, was required to maintain blood pressure in the range of 170/70 to 220/105 mm of mercury. A phentolamine infusion was added on the first postoperative day. Due to limited supply of this agent the rate of infusion never exceeded 0.5 mg per minute. In addition, 0.5 to 1 mg of propranolol was administered intravenously every two hours starting on the second postoperative day to suppress ventricular ectopia and widened pulse pressure which had developed. This combination of agents effectively decreased blood pressure to between 150/60 and 170/80 mm of mercury. Daily dialysis continued during this interval and resulted in a cumulative weight loss of 2.3 kg. At no time were thiocyanate levels in the toxic range.

As a result of a persistent post-operative ileus, oral clonidine therapy was not started again until the seventh postoperative day when 0.4 mg was administered twice a day by mouth. Once clonidine therapy was started again the dose of nitroprusside was decreased and eventually discontinued over the next 24 hours. The remainder of the hospital course was benign and by the 14th postoperative day the patient's blood pressure was 130/70 mm of mercury without administration of antihypertensive medication. Serum catecholamine levels were obtained on the 4th, 8th, and 14th postoperative days; these were 5,338 pg per ml, 713 pg per ml and 213 pg per ml, respectively, (normal 325 to 600 pg per ml).

Peripheral vein renin activity measured on the second postoperative day was undetectable.

Discussion

Severe hypertension developed in the postnephrectomy period, and it was necessary to use potent antihypertensive drugs for several days. The initial blood pressures were significantly higher than those previously observed, either before or during dialytic therapy. Mild hypertension occasionally occurs after nephrectomy and this is thought to be related to hypervolemia, operative stress and pain. Hypertension in this case, however, could not be attributed to hypervolemia because pulmonary capillary wedge pressures were between normal and low. Also adequate analgesia failed to lower blood pressure.

Blood pressure began increasing rapidly 8 to 12 hours after the last dose of clonidine. Of particular significance were the extremely elevated catecholamine levels for the first eight postoperative days. Both these findings are consistent with the clonidine withdrawal syndrome. Epinephrine and norepinephrine are elevated as a metabolic response to surgical operation, but these levels are considerably lower and transient. The possibility of pheochromocytoma was considered remote because of previously normal vanillylmandelic acid and metanephrine urinary screens. Neither propranolol nor minoxidil withdrawal has been associated with a rebound phenomenon.

There probably was an increased risk of clonidine withdrawal syndrome developing in this patient. Hoobler's studies[16] have indicated that this syndrome is more apt to occur when the dose of clonidine exceeds 1.2 mg per day. Strauss and co-workers[15] reported three cases of high renin renovascular hypertension in which severe rebound hypertension developed upon withdrawal of clonidine though 1.0 mg and less per day was administered to the patients. Strauss and co-workers suggested that there may be an increased risk of this syndrome developing in patients with renovascular hypertension, and they proposed a mechanism of renin rebound to account for this phenomenon. Although the peripheral vein renin levels in our patient were elevated preoperatively, postoperative renin activity was undetectable when significant hypertension continued. The extreme level of catecholamines appears to be the sole pressor mechanism responsible for the sustained hypertension. Initially, though, residual renin activity may have served to potentiate hypertension.

The management of clonidine withdrawal has been described.[12,13] Nitroprusside, phentolamine and β-blockers were all successfully used in our case. It would seem that cyanate toxicity was effectively prevented with dialysis. Of note is that reinstitution of oral clonidine therapy reduced blood pressure to normal within 24 hours, and cessation of clonidine therapy three days later did not result in another rebound phenomenon. This suggests that several days or months may be required to establish an environment within the central nervous system that is favorable for rebound phenomena to occur.

The severe and sustained hypertension in this case was attributed to the clonidine withdrawal syndrome, and this is the first report of a case with a postnephrectomy complication. Despite three days of controlled reduction in dosage, rebound hypertension followed complete drug withdrawal. We recommend a considerably longer period of withdrawal preoperatively, as well as catecholamine depletion with reserpine. Fortunately, hypertension, if it occurs, can be managed successfully postoperatively with nitroprusside, phentolamine and propranolol.

Summary

Severe hypertension was encountered in a patient following bilateral nephrectomy for control of renin-mediated hypertensive disease. The rebound hypertension was attributed to clonidine hydrochloride withdrawal and occurred despite gradual preoperative removal of the drug. This is the first reported case of the clonidine withdrawal syndrome complicating bilateral nephrectomy. The anephric state indicates that any contribution by the renin angiotensin system to the development of rebound hypertension is unlikely and implicates excess catecholamines as the sole pressor mechanism. Rapid and prolonged control of blood pressure was obtained through the use of α-blockers or β-blockers, sodium nitroprusside and dialysis.

REFERENCES

1. Smet G, Hoobler SW, Sanbar SL, et al: Clinical observations on a new antihypertensive drug, 2-(2,6-dichlorphenylamine)-2 imidazoline hydrochloride. Am Heart J 77:473-478, 1969

2. Hoobler SW, Sagastume E: Clonidine hydrochloride in the treatment of hypertension. Am J Cardiol 28:67-73, 1971

3. Davidov M, Kaboviatos N, Finnerty FA: The antihypertensive effects of an imidazoline compound. Clin Pharmacol Ther 8:810-816, 1967

4. Onesti G, Schwartz AB, Kim KE, et al: Antihypertensive effect of clonidine. Circ Res 28(Suppl 2):53-69, 1971

5. Parsons WB Jr, Morledge JH: Antihypertensive effect of a new imidazoline compound (clonidine) and chlorthalidone, individually and in combination. Am J Cardiol 26:258-261, 1970

6. Kobinger W: Pharmocologic basis of the cardiovascular ac-

tions of clonidine. *In* Onesti G, Kim KE, Moyer JH (Eds): Hypertension: Mechanisms and Management. New York, Grune and Stratton. 1973, pp 369-380

7. Kobinger W, Walland A: Investigations into the mechanism of the hypotensive effect of 2-(2,6-dichlorphenylamino)-2-Imidazoline-HCL. Europ J Pharmacol 2:155-162, 1967

8. Haeusler G, Finch L, Thoenen H: Central adrenergic neurones and the initiation and development of experimental hypertension. Experientia 28:1200-1203, 1972

9. Finch L: The central hypotensive action of clonidine and BAY 1470 in cats and rats. Clin Sci Mol Med (Suppl) 148:273s-276s, 1975

10. Onesti G, Paz-Martinez V, Kim KE, et al: Effect of clonidine on renin release. *In* Onesti G, Kim KE, Moyer JH (Eds): Hypertension: Mechanisms and Management. New York, Grune and Stratton. 1973, pp 405-409

11. Weber MA, Case DB, Baer L, et al: Renin and aldosterone suppression in the antihypertensive action of clonidine. Am J Cardiol 28:825-826, 1976

12. Hansson L, Hunyor SN, Julius S, et al: Blood pressure crisis following withdrawal of clonidine (Catapres, Catapresan), with special reference to arterial and urinary catecholamine levels, and suggestions for acute management. Am Heart J 85:605-610, 1973

13. Hunyor SN, Hansson L, Harrison TS, et al: Effects of clonidine withdrawal: possible mechanisms and suggestions for management. Br Med J 2:209-211, 1973

14. Reid JL, Wing LM, Dargie HJ, et al: Clonidine withdrawal in hypertension—Changes in blood-pressure and plasma and urinary noradrenaline. Lancet 1(8023):1171-1174, 1977

15. Strauss FG, Franklin SS, Lewin AJ, et al: Withdrawal of antihypertensive therapy—Hypertensive crisis in renovascular hypertension. JAMA 238:1734-1736, Oct 17, 1977

16. Hoobler SW, Kashima T: Central nervous system actions of clonidine in hypertension. Mayo Clinc Proc 52:395-398, 1977

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Thrombocytopenia Associated With Intravenous Heroin Abuse

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ALTHOUGH multiple medical complications are associated with the intravenous injection of illicit drugs,[1-3] thrombocytopenia has only recently been reported.[4] In only two years we have encountered four cases of intravenous heroin abuse in which patients presented with blood loss due to severe thrombocytopenia. In only one patient was there evidence of concurrent infection. A representative case follows.

Reports of Cases

A 19-year-old man (Case 1, Table 1) was admitted to University Hospital with a ten-day history of easy bruising, blood loss from mucous membranes, melena and hematuria. He had intermittently used heroin intravenously and cocaine for about two years. Results of physical examination showed a temperature of 38.2°C (100.8°F), purpura, petechiae and a palpable spleen tip. Laboratory data included a normal leukocyte count and a platelet count of 1,000 per cu mm. The patient's fever abated in one day without therapy. Administration of prednisone, 100 mg per day, was begun and the platelet count returned to normal levels in ten days. A bone marrow biopsy showed an increase in megakaryocytes and normal cellularity. Prednisone was tapered to 60 mg per day over one week, but thrombocytopenia returned (Figure 1). The patient said he no longer was abusing drugs. Reinstitution of prednisone therapy at 100 mg per day resulted in a return of the platelet count to normal levels in seven days; however, thrombocytopenia recurred during administration of steroids. Splenectomy was done and prednisone again tapered. The platelet count was 276,000 per cu mm when the patient was seen in a follow-up examination 18 months later.

A summary of the clinical characteristics of the four patients we saw is shown in Table 1. As in most cases of drug abuse the patients were young and had used multiple drugs for several years.[1] In case 4 concomitant staphylococcus sepsis was present, but findings on examination for disseminated intravascular coagulation were normal. Although thrombocytopenia may be present in patients with acute bacterial endocarditis, it is an unusual presenting manifestation of this disorder.[5]

In one patient (Case 3) there was a positive radioimmunoassay for hepatitis B antigen but all other liver function tests gave normal findings at the time of presentation. Five weeks later, thrombocytopenia recurred while the patient was on a regimen of 20 mg of prednisone per day. The patient denied intravenous abuse of drugs but admitted to excess intake of alcohol. Findings on

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liver function tests were elevated at the time of relapse. Prednisone therapy had been started again, at a dosage of 100 mg per day, and the platelet count was rising when the patient left the hospital against medical advice.

In all four of the patients bone marrow studies had been done on admission and no evidence of toxic alcohol effects was found.

Table 2 shows the responses to treatment. In all cases prednisone therapy, 80 to 100 mg given orally per day, was begun on admission and continued until the platelet count rose to normal. The platelet count increased to 100,000 per cu mm in all patients receiving initial steroid therapy. In two, relapses occurred when administration of steroids was tapered, but the platelet count increased rapidly to normal levels with administration of higher doses of steroids.

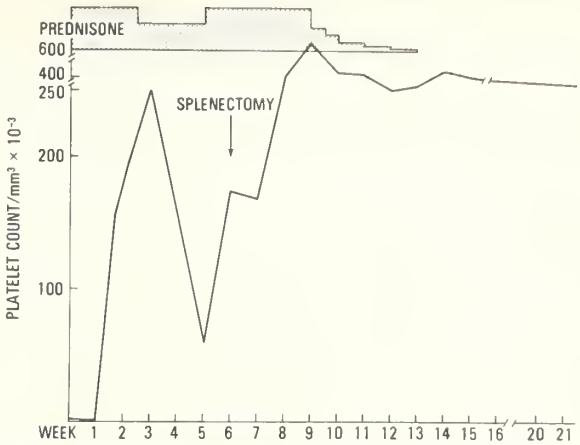

Figure 1.—Peripheral blood platelet counts and clinical course in patient 1 with heroin-associated thrombocytopenia.

Discussion

Adams and co-workers have recently reported five cases of thrombocytopenia associated with the use of heroin.[4] These cases differ in some respects from the four we encountered. Three of their patients were seen in four days and these authors postulated that there had been a common exposure to some toxic element, possibly "brown" heroin. Our four patients were seen during a period of two years. Although "brown" heroin has been in common use in San Diego during this time, we cannot implicate it as a common factor in our four cases.

The cause of thrombocytopenia in these cases is unclear. Most intravenous drug abusers are constantly exposed to multiple illicit drugs, adulterants (including quinine),[1] and bacterial and viral antigens that might be associated with thrombocytopenia. The clinical course in at least two of our patients resembled autoimmune thrombocytopenia;[6] in both of these patients relapse occurred during a period of steroid therapy. One patient may have benefited from splenectomy and has a normal platelet count after all therapy has been stopped. Whether the two relapses were due to a continuing immune response or to resumption of drug abuse is unknown. Other authors[8] have noted immunologic disturbances in heroin abusers, but the relationship of these observations to the thrombocytopenia observed by Adams and by us remains conjectural. The recurrent exposure to illicit drugs, however, can

TABLE 1.—*Characteristics of Intravenous Drug Abusers With Thrombocytopenia*

Case	*Age*	*Presenting Complaint*	*Duration of Drug Abuse*	*Drugs*	*Splenomegaly*	*Bone Marrow Megakaryocytes*
1	19	Epistaxis Purpura Melena Hematuria	Two years	Heroin Cocaine	Tip palpable	Increased
2	27	Gum bleeding Petechiae	Ten years	Heroin Alcohol	Absent	Increased
3	25	Ecchymosis	Seven years	Heroin Alcohol Propoxyphene hydrochloride (Darvon) Methaqualone (Quaalude) Chloral hydrate	Absent	Increased
4	29	Gum bleeding Purpura	Eight years	Heroin Alcohol Meperidine hydrochloride (Demerol) Diazepam (Valium) Codeine	Absent	Increased

TABLE 2.—*Response to Therapy in Patients With Thrombocytopenia*

Case	*Treatment*	*Time to Reach a Platelet Count >100,000 per cu mm on Initial Steroid Therapy*	*Outcome*
1	Steroids Splenectomy	10 days	Relapsed when administration of steroids was tapered; responded to readministration of steroids in seven days; platelet count now normal 18 months after splenectomy; all medications stopped
2	Steroids	10 days	Platelet count normal one month after presentation; all medications stopped
3	Steroids	6 days	Responded initially to steroid therapy but relapse occurred when steroid therapy was discontinued; responded to readministration of steroids within 13 days, lost to follow up
4	Steroids	30 days	Platelet count normal after 24 months; all medications stopped

never be ruled out with certainty in cases of drug abuse.

Enough similarities exist between our patients and those in the report by Adams to indicate that the association between heroin abuse and thrombocytopenia is a real one. In our cases and those of Adams there was a sudden onset of mucous membrane and cutaneous blood loss. Little evidence of concomitant infection was present in three of our four patients and in those previously reported. In three of our four cases, and in four of five of Adams' cases, platelet counts returned to normal within ten days after steroid therapy was started. Adams noted relapses in three of five patients when administration of steroids was tapered, and relapse occurred in two of our four within five weeks after initial diagnosis, while high doses of prednisone were still being given. Whether protracted steroid therapy—as in immune thrombocytopenia—or short-term therapy—as in drug-induced thrombocytopenia—should be used in these cases is unknown. Thrombocytopenia, however, should be added to the list of medical complications associated with intravenous heroin abuse.

Summary

In a period of two years four patients were seen with severe thrombocytopenia associated with intervenous heroin abuse. All were young, all had abused multiple drugs and all presented with mucocutaneous bleeding. In three of the patients there was an initial response to steroid therapy with a rise in platelet count to the normal range within ten days. In two of these patients, recurrent thrombocytopenia occurred when steroid therapy was discontinued, indicating a continuing process. Both denied continued intravenous abuse of drugs. In two the platelet count is now normal after all medication has been stopped and in a third the platelet count is normal after all medication has been stopped and after splenectomy. The cause of this complication is unclear, but thrombocytopenia should be added to the growing list of medical complications associated with intravenous abuse of heroin.

REFERENCES

1. Sapira JO: The narcotic addict as a medical patient. Am J Med 45:555-588, 1968

2. Richter RW (Ed): Medical Complications of Drug Abuse. San Francisco, Harper and Row, 1975

3. Louria D: The medical complications of drug abuse, *In* Glatt MM (Ed): Drug Dependence—Current Problems and Issues. Baltimore, University Park Press, 1977, pp 149-165

4. Adams WH, Rufo RA, Talarico L, et al: Thrombocytopenia and intravenous heroin use. Ann Intern Med 89:207-211, 1978

5. Kaye D: Changes in the spectrum, diagnosis and management of bacterial and fungal endocarditis. Med Clin N Am 57:941-957, 1973

6. Aster RH: Thrombocytopenia due to enhanced platelet destruction, *In* Williams WJ, Bentler E, Erslev AJ, et al (Eds): Hematology. San Francisco, McGraw-Hill, pp 1342-1359, 1977

7. Brown SM, Stennel B, Taub RN, et al: Immunologic dysfunction in heroin addicts. Arch Intern Med 134:1001-1006, 1974

8. Husby G, Pierce PE, Williams RC Jr: Smooth muscle antibody in heroin addicts. Ann Intern Med 83:801-805, 1975

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The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Canadian Cooperative Trial on Platelet-Inhibiting Drugs

To the Editor: In the March issue there appears a review article by Dr. H. I. Machleder on "Strokes, Transient Ischemic Attacks and Asymptomatic Bruits." It includes a discussion of the Canadian Cooperative Trial on Platelet-Inhibiting Drugs which is erroneously referenced and erroneous in substance.

The author states that the study consisted of the administration of "placebo, aspirin, aspirin with dipyridamole or dipyridamole alone." Dipyridamole was *not* used in this study. The drugs used were placebo, aspirin, aspirin with sulfinpyrazone (Anturan), or sulfinpyrazone alone. The accurate reference from which he has derived these misquoted data is given below[1] as is the reference to the major report in which the data were presented in their original form.[2] The reader of the review would be unable to identify this error because of the imperfection in the referencing.

No trial has yet been concluded that tests the benefit of aspirin with dipyridamole. Such a trial is now underway involving ten American and Canadian centers in a collaborative study. There is reason to have some optimism about the combination because the drugs act by different mechanisms. It would appear that dipyradamole (Persantin) acts by interfering with phosphodiesterase and increases cyclic AMP at the platelet membrane. It is probable that aspirin operates by the mechanism described by Dr. Machleder in the review article mentioned. Furthermore, there is *in vitro* evidence that synergism exists between dipyridamole and aspirin. In patients with arteriosclerotic lesions where the platelet survival time has been reduced, Harker and Slichter[3] were able to determine that there was a return towards normal platelet survival time with the administration of dipyridamole and that aspirin alone did not alter the platelet survival time but that the combination of these two drugs brought the platelet survival time to normal.

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REFERENCES

1. The Canadian Cooperative Study Group: A randomized trial of aspirin and sulfinpyrazone in threatened stroke. N Engl J Med 299:53-59, Jul 13, 1978

2. Barnett HJM, McDonald JWD, Sackett D: Aspirin—Effective in males threatened with stroke (Editorial). Stroke 9:295-298, 1978

3. Harker LA, Slichter SJ: Arterial and venous thromboembolism: Kinetic characterization and evaluation of therapy. Thrombos Diathes Haemorrh 31:188, 1974

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Dr. Machleder Replies

To the Editor: Dr. Barnett is absolutely correct in his astute observation. The error was inadvertent, and the drug used in the Canadian Cooperative Trial was indeed sulfinpyrazone and not dipyridamole.

The results of trials with aspirin and dipyridamole will be anxiously awaited from the outstanding group of investigators in Ontario.

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VD in China

To the Editor: There have been many references in the medical and popular press to the supposed elimination of venereal disease in China. The article by Dr. Shulman in the May issue (Shulman AG: Absence of venereal disease in the People's Republic of China. West J Med 130:469-471, May 1979) is an example.

That the incidence of venereal diseases in China has been greatly reduced is probably true, and is certainly a significant public health achievement. However, let us not be naive enough to assume that these diseases have been eliminated

in that country as a public health problem. What undoubtedly exists in China is a lack of adequate communicable disease surveillance and reporting, just as we see throughout the world, including much of the United States. It is often politically fashionable and expedient to deny existence of a public health problem to outsiders.

In the United States in 1978 there were 21,681 reported cases of primary or secondary syphilis and a million cases of gonorrhea. Eight states accounted for 75 percent and 50 percent of these cases, respectively. Between March 1976 and December 1978, there were only 508 reported cases of penicillinase resistant gonorrhea in the nation, of which 289 were from California. Thus, many of the nearly 400,000 practicing physicians in the United States can also say they see very little or no syphilis or gonorrhea in their practices. Fortunately, our medical schools have not used their lack of teaching cases as an excuse to stop teaching about venereal disease.

The commentary coming out of China sounds like the talk of venereal disease eradication in the United States during the middle and late 1950's. In 1957, only eight cases of infectious syphilis (mostly secondary) were reported for the million people residing in Seattle-King County and many areas of the country had no cases, despite the continued existence of prostitution. I doubt whether the Chinese have solved the problem of homosexual transmission of venereal diseases and I question if they have a lesser problem with antibiotic resistant gonorrhea than we do. Furthermore, many Chinese females and males probably also develop asymptomatic infections of gonorrhea and syphilis and do not know they are infected. Venereal disease is likely to remain a public health problem worldwide for years to come.

MAX BADER, MD, MPH
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Thoughts After Three Mile Island

To the Editor: One is fascinated by the recently popular discovery that we arise from previous generations. We are beginning to feel strongly that we have roots in the past. The biological mysteries of intimate blood relationships with men and women and children who precede us, entrance us.

We are beginning to know that our lives and the facts that we can love and breathe and laugh and cry, that we can help and touch one another, that we can hold a baby in our arms and that we can hear the ocean in a seashell—all these and all other sensations that we might have, we have received from those who went before us. From our roots.

We are sad about any suffering that our ancestors might have endured, feel puzzled and perhaps a little guilty at the pain that they might have inflicted on others, individually or during war and holocaust, and wonder at the fact that so many of our antecedents often suffered as a result of the selfishness and arrogance and greed of a few.

Now we are at the watershed. The fact of man-made alterations of the environment on a massive and accelerating scale, has put our generation in a critical relationship to future generations.

Above all looms the threat of radiation concentrated or created by man. No other environmental threat is more fraught with hazard to us and to those whose roots we are and will have been 5, 10, 20, 100 generations from now.

Between 1898, when the Curies discovered radium and its phenomenal property of radioactivity, and the year 1938, just before World War II, the total world supply of radium was less than 600 grams (1⅓ pounds), an amount that would not make a 2-inch cube. Of this, 225 grams were in the United States. The tiny quantity each fortunate hospital in the world might have owned for therapeutic purposes was guarded with an almost ritualistic reverence because of a mixture of respect for its healing properties and concern because of the danger of the invisible and potent radiation that it was constantly emitting.

Now, as a result of nuclear weapons programs and nuclear power plants, we have produced thousands of billions of grams of equally radioactive substances such as plutonium and strontium and tritium and iodine and carbon and xenon and krypton and on and on. And while we wonder what we are to do with this deadly cargo that for generations can cause cancer and can deform the genetic heritage that we carry within us, we keep cooking up our witches' brew as if we have gone mad.

The atom, this tiny particle of matter which we must imagine in our minds because we cannot see it, dominates the minds of many and has infected the brains of our leaders, much as if it were a virus. It has bred ideas of arrogance which make us believe that we can forever dominate nature;

this virus of the atom has bred greed to go along with our arrogance of power, so that we believe in our concept of never-ending growth, as if we ourselves have become a cancer on the planet.

Where are the statesmen who would have the courage to say: Let us now pause. Let us be humble before nature. Let us be silent for a moment and let us listen. Perhaps we will be able to hear the voices of generations yet unborn, thanking us for our wisdom, expressing their gratitude to us for pausing a while, for having the courage to admit that we are lost on a dark and dangerous trail, and for having the good sense to be cautious.

Let us recall the words from the Russell-Einstein Manifesto, read by Bertrand Russell on July 9, 1955:

> There lies before us, if we choose, continual progress and happiness, knowledge, and wisdom. Shall we, instead, choose death, because we cannot forget our quarrels? We appeal, as human beings, to human beings: remember your humanity, and forget the rest. If you do so, the way lies open to a new Paradise; if you cannot, there lies before you the risk of universal death.

Let us remember our humanity, and forget the rest.

How little we will lose, and for such a short time, if we would just pause. But by not attending to the cancer of growth and more growth, very soon we stand to lose everything in a final firestorm. Whose roots will we then have been?

ANDRÉ BRUWER, MD
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Patient Care Audits

TO THE EDITOR: The letter of Thomas Wynn in the May issue (Patient Care Audits Not Cost Effective) raises an excellent point concerning patient care audits.

For these audits to be effective, either as a teaching aid or in reducing costs, physicians must make the same mistake repeatedly in the care of patients or many physicians must make the same mistake. This simply is not realistic. On those occasions where mistakes occur, they will continue to occur as they always have—a given physician caring for a given patient will either fail to do something he should or do something he should not. All of the patient audits that have ever or will ever be done could not correct this.

Out of curiosity several years ago, we set aside one month in the city of Glendale, California, and monitored the number of hours donated by physicians on hospital staffs in those functions not directly related to patient care. We had the man-hours donated for committee meetings and staff meetings tallied, specifically excluding the additional hours given by the officers of the staff and also excluding all educational activities. In the four major hospitals in Glendale, we averaged more than 300 man-hours per hospital per month donated in noncare services. This is, for the most part, wasted time. It is difficult to consider any other field in which this amount of time and effort would be donated gratis. As long as we are willing to do so, I believe the demand will increase endlessly. Only when the profession as a whole takes the stand that Dr. Wynn and I have taken in refusing to pursue these exercises of futility will they finally come to the end they so richly deserve.

GORDON BREITMAN, MD
Glendale, California

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TO THE EDITOR: As chairman of the Quality Assurance Committee for the San Francisco Peer Review Organization (SFPRO), I would like to respond to the points raised in Dr. Thomas Wynn's letter in the May issue (Patient Care Audits Not Cost Effective).

First, many San Francisco physicians share his concern that some medical audit programs do not have an impact on quality of care and are nonproductive activities. However, there are mechanisms in place in some San Francisco hospitals which make this activity fruitful and meaningful for medical staffs, without an inordinate expenditure of time or money. By focusing on quality of care *problems* as the basis for audit topics, limiting the number of criteria items to a maximum of ten and audit samples to 20 to 30 cases, the costs of performing medical audits are substantially reduced. It is then the responsibility of the hospital medical staff and governing body to take corrective action and monitor those actions when quality of care problems are identified. This can occur in the majority of audits performed if actual or perceived problems are chosen at the outset of an audit study. This is why SFPRO is pushing the concept of generic screening (problem-oriented audit), which is being taught at the California Medical Association/California Hospital Association Audit Workshops.

It is unfortunate that Dr. Wynn's experience

as an audit chairman was so disappointing. Perhaps if quality of care problems had been reviewed, rather than the top ten common diagnoses and procedures, this experience would have been more productive. The ratings quoted are accurate. These are not government ratings; rather, they are assessments by peer physicians. However, the hours that were reported for the University of California in San Francisco are not reflective of the studies reviewed by SFPRO.

Finally, audit or something like it will doubtless always be with us because of our professional need to assess quality. We must make it work. In large part, this will determine the success of the PSRO program, in which each of us has a heavy stake because it may be our last chance to regulate ourselves.

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Preventing Dental Caries in Children

TO THE EDITOR: As physicians we pride ourselves on our successes in preventive medicine. Polio has been conquered, tuberculosis is no longer the white plague, our drinking water is pure, milk is pasteurized, and we are backing compulsory immunization for school children. But we in the medical profession have failed in one very important aspect of preventive medicine relating particularily to our younger generation, and that is the prevention of dental caries.

Our quick reply is "But that's the responsibility of the dental profession." Indeed, that was my attitude until a recent and rather prolonged session at my friendly dentist's office, where I had the opportunity of delving into some of his professional publications. The following are just a few disturbing facts that I came away with: (1) Dental disease is without question the most prevalent unmet public health problem in our country today. (2) Infants and children need supplemental fluoride from the day they are born up to age 8 if they are to have good dental health in their adult years. (3) At least half of the 44 million Americans who are now wearing dentures could have been spared the cost, pain, trouble and indignity of false teeth had they been given supplemental fluoride in the first eight years of life. (4) Because we think of the *baby teeth* as only temporary little pearls to be given to the *tooth fairy,* we may overlook the fact that they are vitally important in the formation of the arch of the jaw to make room for the proper alignment of the erupting permanent teeth. Poor dental health in the first five years of life can result in malocculsion, misshapen teeth and many expensive trips to orthodontists.

Now where do we physicians come into the picture? Why is it our responsibility, rather than solely that of the dental profession? The obvious answer is that physicians see and care for infants and children long before they are ever seen by a dentist.

It is estimated that 20 percent of the calcification of infants' teeth occurs *in utero,* and that the remaining 80 percent of their mineralization is completed in the first year of life. Moreover it is in the first five years of life that the permanent teeth receive their initial hard coat of enamel, if they are ever going to get it. Who among us takes their children to a dentist before age 5?

Those parents—and physicians—living in areas where the water supply is fluorinated may be lulled into a false sense of security. Breast-fed infants, for example, get far less than the daily minimum requirement of fluoride. And how many youngsters really drink water? In my experience they get their supply of liquids by way of milk or soft drinks—all surely lacking in fluoride. Obviously, here there is a crying need for supplemental fluoride.

Those living in communities supplied with nonfluorinated water have an even greater responsibility to our young patients. First, we must dissuade parents from the fear that fluoride is poison. Dr. Harold C. Hodge of the University of California in San Francisco has done a painstaking demographic study showing that there is absolutely no difference in the public health statistics in nonfluorinated communities as compared with those that have fluoride in their water supply. Illness, injury and death rates are comparable. Moreover, there is no evidence that fluoride can cause sensitization, or that it is mutagenic.

Where else in the practice of preventive medicine can we achieve such a remarkable benefit for future generations as we can by making certain that our new generation of infants and children get their daily minimal dose of fluoride? As I look in the mirror while brushing my teeth I observe the hundreds of dollars of dental work in there, and then and there I renew my resolve to nag, coerce, even browbeat each mother with

the question "Is your young one surely getting a daily dose of good-tooth medicine?"

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Of Politics, Smoke Screens and Industry

TO THE EDITOR: In the May issue I was delighted to read the editorial "Politics and Health Care Smoke Screens," disclosing the smoke screens that pervade almost the entire spectrum of political activities. These are by no means a recent innovation, but extend over more than four decades.

The rise of medical care costs is being restrained but how much of a substantive remedy has been implemented to cure the sick dollar? There is, of course, some slight merit psychologically to restrain wages and prices. Furthermore, many of us agree with the aim of lower costs, but the effects of self-controlled (voluntary) cost reduction will pale to insignificance when forces outside of the hospital do not contribute to a similar objective.

There is, by general agreement, "something extra-commercial about medicine" but a recent, now widely popularized, political smoke screen denies the singularity of life and reverence for life and health—beliefs to which the public obstinately holds. There was something very disquieting when the chairman of the Federal Trade Commission stated (quoted in *American Medical News,* August 8, 1977) that ". . . the delivery of health care is business, an industry of vast proportions. . . . Health care has become our [sic] business. . . ." What was the pretext for such a new approach? It was ". . . one possible way to control the seemingly uncontrollable health sector . . . [by treating it] as a business and make it respond to the same marketplace influences as other American business and industries." There you have it in a nutshell—the circumventing means used to initiate government intervention.

And what was the response of the American Medical Association to this use of the term "health industry?" The *American Medical News* (February 6, 1978) noted that ". . . recent research indicates that medicine is being perceived as an industry. . . ." and the AMA Executive Vice President is quoted as saying "Health care is an industry. It is, in fact, the first or second largest industry in the country. We have a product, a purchaser, and a price. That's all you need to conduct a marketing operation."

It is ironic that leaders of organized medicine lend support to such a pejorative implication, disregarding its connotation of profit. The composite work of the medical professionals is not "industrial," nor is the product of their service a result that can be labeled an "industrial product" or "industrial output." Such usage, now widely popularized, lacks precise meaning in medical care. By conceding in the use of such terms, the AMA provides a wedge through which a premise is validated and the practitioners in medicine and nursing are disadvantaged. Medicine, thereby, is caught in a semantic trap in its defense against the contentions of the Federal Trade Commission.

This is a matter of no small importance. It leads to an erosion of our concept of medical care provision and an erosion of the authority of professionalism of medical and nursing providers, and of hospitals. The concept of medical care as not an "industry" is central to its preservation. All this does not deny the need of a balanced commitment to some retrenchment in medical care costs, but it also recognizes the growing mischief of lack of concern of some of our leaders with the ideal—the worth of human health and life—by emphasizing only the partiality of money.

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Refer to: Guidotti TL: Health implications of increased coal use in the western states (Environmental Health). West J Med 131:70-76, Jul 1979

Health Implications of Increased Coal Use in the Western States

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The National Energy Plan proposed by President Carter provides for the rapid development of coal resources in the United States, particularly in the West. The potential consequences for health of this development were considered by the Advisory Committee on Health and Environmental Effects of Increased Coal Utilization, reporting to the Department of Energy. Their report recommended rigid adherence to pertinent existing regulations, improved environmental monitoring, expanded research in selected relevant topics and development of procedures for selecting the sites of new coal-fired power plants. Although the report was a major exercise in technology assessment, it is fundamentally a cautious document that proposes no new solutions or approaches. A review of occupational and community health problems associated with coal mining and coal utilization suggests that lessons from past experiences, especially in Appalachia, cannot be applied to the West uncritically. The two regions are fundamentally different in scale, topography and social development. In the West, future problems related to coal are likely to derive from unknown risks associated with coal processing technologies, land reclamation and water quality at the sites of power generation, and extensive social and demographic changes at centers of industrial activity that may have secondary effects on health. Additional considerations should supplement the recommendations of the Advisory Committee report.

A MAJOR COMPONENT of the National Energy Plan proposed by President Carter is the rapid development of American coal resources. The conversion of industries and utilities from oil to coal as a source of energy is already well under way.[1]

When petroleum dominated the national energy budget, little incentive existed to invest in new coal mines or to expand the capacity of existing coal-handling facilities. With the current new wave of interest, the push is on to develop previously unmined coal fields in the Western states. Most of this coal will be used to supply utilities serving Western cities.[2] Such a massive shift in energy production will have far-reaching effects on the region. Among the most important but least predictable of these effects will be the impact on health in the West.

An economic activity of this magnitude is

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ABBREVIATIONS USED IN TEXT

CWP = coal workers' pneumoconiosis (black lung)
PMF = progressive massive fibrosis

bound to have potential consequences for environmental and occupational health. Although there is no accepted systematic methodology for assessing the probable effects of introducing such a technology into a region on a massive scale,[3] preliminary plans must be made by federal and state authorities to anticipate problems. The Department of Energy has had the assistance of a panel of advisors chaired by Dr. David Rall, Director of the National Institute of Environmental Health Sciences. This Advisory Committee on Health and Environmental Effects of Increased Coal Utilization recently published its final report in the *Federal Register*.[4] The document is a major effort in technology assessment and is well worth studying critically.

The Advisory Committee report recommends several federal measures to minimize the emergence of health problems resulting from expanded coal utilization in the United States. These are summarized below:

- Require rigorous adherence to federal and state air, water and solid waste regulations with the universal adoption and operation of the best available control technology.
- Require rigorous adherence to reclamation standards and sponsor small-scale demonstration projects.
- Require rigid adherence to mine health and safety standards, development of a systematic health monitoring and assessment program for mine workers, and close monitoring of training and safety programs for new mines.
- Improve environmental monitoring and data collection in the United States.
- Expand research programs in (1) air pollution chemistry, distribution, toxicology, (2) the atmospheric effects of carbon dioxide, (3) acid fallout (from air pollution) and its biological effects and (4) the migration of toxic trace elements.
- Develop procedures for the *judicious* siting of coal-fired facilities.

The Advisory Committee report was an important exercise in technology assessment and environmental health. The main thrusts of the recommendations are to support the enforcement of existing regulations and to urge further research. While this provides useful support to agencies and individuals presently struggling with a difficult and complex problem, nonetheless it urges a cautious policy that misses many opportunities for creative new solutions and for public education and participation. Such creative approaches suggest themselves after a critical review of health problems associated with coal mining, coal combustion and coal-dominated communities.

TABLE 1.—*The Magnitude of the Expansion of Coal Mining in Far Western States*[5,6]

State	Number of Existing Mines*	Number of Planned New Mines	Annual Coal Production†	Increases in Production
Arizona	2 (0)	0	10.2	5.0
Colorado ...	33 (18)	37	9.4	45.6
Montana ...	8 (0)	6	26.1	48.2
New Mexico .	5 (1)	3	9.8	77.7
North Dakota	10 (0)	5	11.1	42.6
Utah	20 (20)	25	7.9	64.5
Washington .	4 (1)	2	4.1	2.0
Wyoming ...	20 (5)	23	30.9	139.8
Total, 8 states	102 (45)	101	109.5	425.4

*Numbers in parentheses indicate underground mines; remainder are strip mines.
†Annual production in millions of short tons per year. A short ton, the industry standard measure, is very nearly equal to a metric ton, or 1,000 kg. Data are current for 1976.

Background to the Problem

To understand the potential importance of health problems associated with increased coal extraction and utilization in the West, one must appreciate the magnitude of the economic commitment.

The estimated increase in coal mining activity in eight Western states is tabulated in Table 1 from data compiled by the Bureau of Mines.[5,6] Between opening new mines and expanding production in existing ones, present plans call for adding almost half a billion short tons (a short ton is almost equal to a metric ton, 1,000 kg) every year for most of the next ten years. Strip mining will predominate throughout the Western coal fields except in Colorado and Utah, where most new mines will be underground. Thus a substantial work force will be exposed to a new set of occupational hazards in the region. Most of the coal mined in the West will be used there by Southwestern utilities and heavy industry.[2] The increase in coal utilization and the introduction of strip mines into a very different ecological

setting raise the possibility of occupational risks and environmental health problems in Western coal communities.

Coal Mining: Occupational Risks

Much less is known about the occupational health effects of strip mining than of underground mining, but this probably reflects the lack of urgency in the past because underground mining has been conspicuously more dangerous. One would expect that strip mining would result in less dust exposure and that the risk of trauma would be less, so that the occupational health risks are probably more akin to those of a quarry or dam construction site. Because of these differences and the improving technology for dust control, one cannot simply extrapolate from the mining experience of Appalachia to the West. Nonetheless, a brief consideration of the known health problems associated with coal mining will provide a framework for discussion.

Patterns of morbidity and mortality among coal miners and residents of coal mining communities have been reviewed in detail recently and will be summarized only briefly.[7]

Coal miners have a life expectancy and overall mortality from all causes that are similar to those for the general adult male population.[8] Paradoxically, this is cause for concern because the selection pressure of their strenuous occupation would be expected to result in a lower mortality than for men in general, a phenomenon known in occupational epidemiology as "the healthy worker effect."[9] This finding suggests a possible aggregate excess mortality that is countering the effect of selecting a population of workers sufficiently fit to perform physically demanding work.

Examining mortality rates by specific causes compared with rates for the general adult male population, coal miners have an increased incidence of mortality from several causes—particularly trauma, respiratory diseases and cancer, chiefly of the stomach. (Lung cancer does not appear to be an occupational hazard for coal miners.[7,10]) Tuberculosis rates in the general population of Appalachia, which has been the principal coal mining region of the United States, have been high for many years, so that reports of elevated risk for death from this cause among coal miners should not be considered as proof of an occupational risk in the absence of silicosis.[7]

The principal respiratory diseases of coal miners are not limited to coal workers' pneumoconiosis (CWP, commonly called black lung), although this is their characteristic occupational disease. Miners are also at risk to develop silicosis, especially if they are involved in mine construction or in certain jobs that require rock drilling. A chronic, irritative bronchitis may develop which has been called industrial bronchitis.[11] CWP itself is a clinical and radiologically diagnosed condition which is classified as *simple,* in which case its functional significance is usually negligible, or *complicated.* Complicated CWP is the radiological description of the pathological finding of progressive massive fibrosis (PMF), in which increasing pulmonary fibrosis forms enlarging nodules and an obliterative endarteritis. Complicated CWP, or PMF, can result in severe respiratory impairment and cor pulmonale, and should be considered a potentially life-threatening disease.[7,11]

There are certain helpful studies that have indicated general regional trends: Underground coal miners in Utah and Colorado have a much lower prevalence of simple CWP than Eastern miners of comparable age and experience, and little or no complicated CWP (PMF).[11] The rank (quality grade) of coal in the West is bituminous or lignite, the dusts of which appear to be much less dangerous than that of anthracite, which predominates in Pennsylvania.[7,11] The dust exposure of surface workers at underground mines is probably comparable to that of strip mine workers. Surface workers have a much lower prevalence of CWP and less frequent abnormalities on pulmonary function tests than underground miners.[11,12] One may, therefore, expect relatively little occupational respiratory disease due to coal mining in the West as long as present safety and health standards are met. *Industrial bronchitis* might be the most likely problem of the three respiratory diseases of coal mining.[7,11] Trauma is likely to be the single greatest occupational hazard. Too little is known of increased cancer mortality to project a trend.

The production of energy from coal in the future will probably not be based on simple combustion of the mined product. Intermediate processing will convert the coal into a form that is more efficient and convenient to transport. The two principal candidates for this intermediate role are gasification[13] and liquification.[14] The National Institute of Occupational Safety and Health has already issued preliminary recommendations for standards to protect worker health in pilot coal gasification plants, but these are largely extrap-

olated from other, similar industrial processes and are not based on new data.[15] Coal liquification is not as far along in its technical development and a full-sized pilot plant does not exist yet in this country.[14] Liquified coal contains an enormous variety of organic compounds reflecting the biological origins of the material,[16] some of which are likely to be toxic or carcinogenic.[15] The toxic hazards posed by the coal processing technologies cannot be adequately anticipated at present. The products of both processes are complex mixtures of aliphatic and aromatic hydrocarbons, sulfides, organic metal compounds, carbon monoxide, and other substances. The processes involve varying degrees of physical containment and hence different risks of exposure. The state of the engineering art is rapidly advancing and with it the compositions of the products and the risks of exposure are changing. Past studies and the experience of other related technologies are uncertain guides to the future risks.[15] Therefore, both technologies deserve close observation to anticipate risks to the health of workers and residents of the local communities in which these plants are to be located.

In summary, occupational health risks resulting from expanded coal mining in the West are unlikely to be as great as they historically have been in the Appalachian experience. Coal processing technologies deserve further study because their risks are not known.

Coal Mining: Community Risks

Community health problems resulting from coal mining may be mitigated by the remote location of most mines. Groundwater contamination by mine seepage could become a serious problem in semiarid regions where alternative sources do not exist and where the water quality may already be poor.[7] The surface water in areas of heavy bituminous mining tends to be acidic and high in sulfates, iron, calcium and trace elements.[17] Substantial treatment may be required to render such water potable if the runoff contaminates groundwater sources or aquifers used by local communities. Many of the mines will be located in arid and semiarid regions where they will compete with local communities for the use of limited water supplies for coal processing and for slurry-mixing to transport coal by pipeline.[18] Dust fallout from nearby mines is bound to occur as well.

The sites of excess cancer mortality among residents of Appalachian communities includes stomach, lip, mouth and throat.[7] Although these are sites that could plausibly be related to an environmental exposure, the risk may result from the common habit of tobacco chewing.[19,20] One cannot predict that coal mining per se will introduce an environmental risk of cancer.

Local community health problems, therefore, may relate primarily to water quality in areas of active coal mining. These problems may be minimized by appropriate reclamation procedures, by protecting area aquifers against contamination by runoff, and by avoiding the construction of residential communities adjacent to or near the mines. Most likely the more significant community health effects of coal mining would be secondary to demographic changes, such as those described below.

Coal Utilization: Community Risks

A major legal and political battle over coal utilization in the Southwest preceded the present rush of interest, but highlighted all of the basic issues. In 1971 a consortium of Southwestern utilities sought to expand power production by developing the enormous Black Mesa strip mine in northeastern Arizona to supply a series of huge power plants in Utah, Arizona, Colorado, New Mexico (collectively called the Four Corners area) and Nevada. The electricity generated was to have been used primarily in Los Angeles, San Diego, Las Vegas, Phoenix and Tucson, and the project would have created thousands of new jobs.* The plan was bitterly opposed by environmentalists and by certain segments of the Hopi and Navajo tribes on grounds of ecological degradation, public health, water rights and religious freedom (the mine occupies sacred tribal land). At the same time, serious questions were raised regarding the benefit of economic development weighed against the risks to health and to the quality of life in the area. The then Executive Director of the Arizona Tuberculosis and Respiratory Disease Association intuitively characterized the demographic implications of the new industry as follows:[21]

Small cities and towns dot the Southwest, charming communities in which to live. Many of the young people who

*Environmental Impact Statements on various phases of the proposed power grid sponsored by the Western Energy Supply and Transmission Association (a consortium of 23 utilities) were filed by the U.S. Bureau of Reclamation, Salt Lake City, 1971, covering the Black Mesa mine, the Navajo Project, the Huntington Canyon Generating Station and Transmission Line, the Navajo-McCullough Transmission Line, and the Navajo-Black Mesa Coal Haul Railroad.

resided in those towns have abandoned them because of the attractions of urban living. Remaining in these towns is an older population. Obviously, the older population is that segment where chronic diseases are most prevalent. They are labelled susceptible. If anyone suffers from adverse effects of air pollution, it will be the older citizen, the susceptible, as well as the American Indian.

The prolonged legal and political dispute ended with the sharp curtailment of the planned power network and cancellation of many units. Even so, the Black Mesa mine continues to deliver about 5 million tons of coal annually to power plants at Lake Mojave, Nevada, and at Page, Arizona.[5]

With such a legacy of conflict, it is surprising that many of the primary belligerents in the Black Mesa/Four Corners battle are now collaborating in the National Coal Policy Project, an effort to find common ground and agreement between environmentalists and industry leaders.[22]

The increasing use of coal combustion to generate electricity will threaten air quality gains in some areas[4] because new coal-burning utilities will be located near population centers rather than near the coal beds.[22] Significantly tighter emissions control standards may be required in the future to maintain air quality at present or improved levels despite increasing combustion by power plants and factories.[23] Recent studies by TRW, Inc., and the Electric Power Research Institute have concluded that the basic technology for coal-burning power generating stations will probably remain substantially the same over the next two decades except for the introduction of intermediate processing. If so, future standards will have to be met by emissions control devices rather than by fundamental changes in the design of the plants. The technologies for removing the oxides of sulfur and particulates from stack emissions are further refined than the technology for removing the third major class of air pollutants encountered in this setting, the oxides of nitrogen. The latter pollutants are likely to be the most stubborn problem in emissions control.

Recent data suggest that the earliest health effects of the oxides of nitrogen in ambient air may be very subtle, such as an increase in the frequency and severity of respiratory tract infections.[24] Furthermore, the combustion products of lignite (brown coal), which is increasingly being utilized for power in Texas,[25] may contain more than 22 elements, including quantities of lead, mercury, cadmium and zinc. Electrostatic precipitators vary in the efficiency of removal of these metals, each of which may have subtle toxic effects.[26] Yet another compelling reason for enforcing strict emissions standards is the recent demonstration of mutagenic (and potentially carcinogenic) substances in respirable particles of fly ash from an electrostatic precipitator in a modern coal-fired power plant.[27] It would be prudent to keep exposure to such substances to an absolute minimum among workers and the general population. Airborne emissions from modern coal-fired facilities may release radionuclides at levels significantly above background levels but low enough that any conceivable health effect would be impossible to detect.[28]

There are no available studies rigorously examining the health effects of a modern coal-fired power station on its local and service communities. A major, large-scale, multiple-site study was recently proposed to compare the impact on community health of conventional fossil fuel and nuclear facilities. Such a study could also be structured to compare oil-fueled and coal-fueled plants. If no elevation in risk was apparent among communities served by a particular type of plant, this result would be important reassurance that a significant threat to health would be unlikely. Until such a study is conducted, the potential health effects of modern fossil fuel power plants on their local and service communities can only be conjectured.[29]

Demographic Changes: Community Health Impact

The Western United States, particularly the rural desert and Rocky Mountain areas where coal production will be concentrated, have some superficial similarities to the Appalachian mountains, the traditional center of American coal mining. The economic and cultural activities are centered in small towns, and medical care—particularly at the secondary and tertiary tiers—may be poorly accessible.[30] Adequate housing and water supplies may be scarce. These and other pertinent community health problems have been described in detail for the rural West[31] and are shared by Appalachia.[7] On the other hand, there are important differences between the two regions: the West has been more affluent, has been more heterogenous in its population and economy, and has experienced an influx of population rather than the outward migration that has characterized Appalachia until recently.[7] Thus despite some superficial similarities morbidity trends of present

coal mining communities cannot be extrapolated to the West uncritically. The situation most comparable to the Appalachian experience is likely to be that of the rural Indian population or other rural minorities. Indians constitute a large fraction, frequently the majority, of the work force in power plants and facilities in parts of the Southwest. The Black Mesa mine, for example, is located on the Hopi reservation and employs many Navajo. Health planners should be aware of the special needs and problems of such communities.[31]

The massive expansion of coal mining, processing and utilization will lead inevitably to a type of community characteristic of the American West—the boom town.[30] This phenomenon was not considered by the Advisory Committee report and is a significant omission.[4]

A boom town is a small, isolated community which suddenly experiences rapid economic development, usually due to the exploitation of natural resources or tourist appeal. The rapid population influx severely strains municipal services (particularly schools), land use planning, mental health clinics and pollution control enforcement. Control over a boom town's growth and development increasingly falls to governmental and economic forces outside the local community structure. These outside forces may not be sensitive to concerns over the adequacy of local services and the quality of life in the community. Studies of these situations have emphasized the economic and crime problems of an expanding population served by a lagging infrastructure (the physical resources and social organization of a community). The work that has been done on this social phenomenon has been based largely on Western coal mining and power generating communities, so that the model is directly applicable to the problem of expanded coal utilization.[32,33] Unfortunately, the health implications of boom towns have not been closely examined.

Given the present high capital costs for providing medical services in small rural communities[31] and the initial drop in *amenity benefits* (level of services to the individual resident proportionate to taxation and revenue) that accompany boom town development,[33] it is clear that medical, public health, sanitation and pollution control services may lag seriously behind economic growth in many coal-dependent boom towns. Preliminary data from Montana suggest that this process of community degradation has already begun, even this early in the development of the state's coal resources.[30]

Public discussion of expanded coal use in the West is now increasing as a result of publicity and political attention.[1,2,22,30] This public debate comes at a time when commercial development and policy execution are already underway, however. There has been no systematic effort to seek citizen response in advance, although the character of the region will be profoundly changed by those developments. In the absence of such preparation, the public debate is only now taking shape. The health implications of these developments are important aspects of the debate.

Lacking specialized public health training and very seldom experienced in regional planning issues, most physicians are ill-equipped to participate in the discussion, even on the local level. This is unfortunate, because the design and planning of communities and patterns of economic use may profoundly affect the health of residents and their access to health care. Trained health professionals with expertise in planning, or a relatively few physicians prepared to become familiar with the discipline of urban and regional planning, might contribute substantially to the planning process and would assist the public debate.[34]

Conclusions

In addition to the formal recommendations of the Advisory Committee report, several supplementary suggestions merit consideration in shaping public policy on Western coal utilization. Most of these suggestions would require federal action, but a few are within the capacity of state and local authorities to implement.

- Much wider public discussion on the issue of expanded coal utilization is needed in the Western states.
- Medical and health professionals should become involved in community and regional planning processes well ahead of the implementation of proposed projects.
- More trained professionals are needed to guide development and to provide epidemiologic and environmental analyses.
- The Environmental Impact Statement, required under the National Environmental Policy Act of 1969, should be refined into a baseline

survey of environmental and health conditions with proposals for monitoring changes.

- A major research effort should be supported to assess the potential health risks of coal processing technologies; that is, gasification and liquification.
- Selected representative Western coal mining communities should be prospectively studied to monitor the health, economic and social impact of coal activities.
- A large-scale epidemiologic survey to compare the community health effects of coal-fired, nuclear and other power stations should be organized and supported.
- Untoward effects of the boom town phenomenon should be considered in formulating policy within the National Energy Plan and assistance should be considered for communities experiencing a disproportionate share of the burden.
- The National Energy Plan should be open to modification if a substantial health problem is encountered.

The National Energy Plan cannot be solely an economic development plan because its effects are too far-reaching in other areas of national life. The social and health effects of its implementation should be anticipated and controlled as well as possible. The Advisory Committee report was an important exercise in technology assessment and environmental health. Perhaps these additional suggestions will bring about further critical discussion of the implications of such massive projects. Much remains to be done to prepare for the coming impact and to channel the development toward constructive ends. The time to prepare is now; the momentum of economic development has already begun.

REFERENCES

1. Pine A: Energy—The U.S. has a national policy, and it's working. Washington Post 100:E1, Mar 19, 1978
2. Smith JP, Sinclair W: Strike complicates shift in policy on tapping coal reserves. Washington Post 100:A6, Feb 25, 1978
3. Guidotti TL: Medicine, critical science, and the real world. West J Med 123:69-70, 1975
4. Committee on Health and Environmental Effects of Increased Coal Utilization: Health and environmental effects of the increased use of coal utilization. Federal Register 43:2229-2240, Jan 16, 1978
5. Corsetino JS: Projects to Expand Fuel Sources in Western States. US Dept of Interior, Circular 8719, 1976
6. Coal Data 1976. Washington DC, National Coal Association, 1977
7. Guidotti TL: Coal workers' pneumoconiosis and medical aspects of coal mining. Southern Med J 72:456-466, 1979
8. Ortmeyer CE, et al: The mortality of Appalachian coal miners. Arch Environ Health 29:67-71, 1974
9. Goldsmith JR: What do we expect from an occupational cohort? J Occupat Med 17:126-131, 1975
10. Costello JS, Ortmeyer CE, Morgan WKC: Mortality from lung cancer in U.S. coal miners. Am J Pub Health 64:222-224, 1974
11. Morgan WKC, Seaton AS: Occupational Lung Diseases, Philadelphia, W. B. Saunders, 1975, pp 165-167
12. Fairman RP, O'Brien RJ, Swecker S, et al: Respiratory status of surface coal miners in the United States. Arch Environ Health 32:211-215, Sep-Oct 1977
13. Maugh TH II: Underground gasification: An alternate way to exploit coal. Science 198:1132-1134, 1977
14. Swabb LE Jr: Liquid fuels from coal: From R&D to an industry. Science 199:619-622, 1978
15. National Institute for Occupational Safety and Health: Recommended Health and Safety Guidelines for Coal Gasification Pilot Plants. Interagency Energy-Environment Research and Development Report, Pub No. 78-120. Rockville, MD, US Dept of Health, Education, and Welfare, 1978
16. Rubin IB, Guerin MR: Fractionation of synthetic crude oils from coal for biological testing. Environ Res 12:358-365, Dec 1976
17. Corbett RG: Effects of coal mining on ground and surface water quality, Monongalia County, West Virginia. Sci Total Environ 8:21-38, 1977
18. Harte J, El-Gasseir M: Energy and water. Science 199: 623-634, 1978
19. Blot WJ, Fraumeni F Jr: Geographic patterns of oral cancer in the United States: Etiologic implications. J Chron Dis 30:745-757, 1977
20. Zacho A, Nielsen J, Cederquist C: Relationship between type of tobacco used and localization of tumor in patients with gastric cancer. Acta Chir Scand 141:676-679, 1975
21. Chaiken B: Testimony, *In* First Session on Environmental Problems Associated with the Production of Power by Coal-Fired Plants in the Four Corners Region (Hearings before the Committee on Interior and Insular Affairs, US Senate, 92nd Congress), Page AZ, May 28, 1971 US Government Printing Office, Washington, DC 1971. Part 5, p 1570
22. Alexander T: A promising try at environmental detente for coal. Fortune, 94-102, Feb 13, 1978
23. Heitner KL: Air pollution assessment of new fossil fuel technologies. J Air Poll Control Assoc 27:1173-1177, 1977
24. Guidotti TL: The higher oxides of nitrogen: Inhalation toxicology. Environ Res 15:443-472, 1978
25. Walsh J: Texas power companies converting from natural gas to coal, lignite. Science 198:471-474, 1977
26. Heinrichs H: Emissions of 22 elements from brown coal combustion. Naturwiss 64:479-481, 1977
27. Chrisp CE, Fisher GL, Lammert JE: Mutagenicity of filtrates from respirable coal fly ash. Science 199:73-75, 1978
28. McBride JP, et al: Radiological impact of airborne effluents of coal and nuclear plants. Science 202:1045-1050, 1978
29. Neyman J: Public health hazards from electricity-producing plants. Science 196:754-758, 1977
30. Christiansen B, Clack TH Jr: A Western perspective on energy: A plea for rational energy planning. Science 194:578-584, 1976
31. Guidotti TL: Health care for a rural minority. Calif Med 118:98-104, 1973
32. Gilmore JS: Boom towns may hinder energy resources development. Science 191:535-540, 1976
33. d'Arge RC, Brookshire DS, Adams RD: Are boom towns bad? Presentation to the Amer Assoc Advancement Sci Annual Meeting, Washington DC, Feb 16, 1978
34. Guidotti TL: Environmental and community planning: A medical concern. The Pharos of Alpha Omega Alpha 35:112-116, 1972

Refer to: Sayre SA: Continuing education: A medical school responsibility? (Medical Education). West J Med 131: 77-81, Jul 1979

Continuing Education: A Medical School Responsibility?

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A survey of medical school deans sheds some light on current attitudes and practices regarding continuing education. The role of medical schools as leaders in continuing medical education should be clarified.

THE HISTORY of medical education in the United States has clearly been influenced by the public's perception of health care needs. The Flexner Report responded to a widely recognized uneven quality of professional care resulting from an unsupervised (and in many instances substandard) system of undergraduate instruction. With this mandate, medical schools developed rigorous criteria for admissions and created a demanding course of study that required total commitment to the process of becoming a physician.

From the knowledge explosion that accompanied and followed World War II came an awakening to the need for specialization in medical education. Emphasis shifted to internship and residency training. Although postgraduate house officer education is accredited in some nonaffiliated hospitals, most teaching hospitals are associated with medical schools which provide varying amounts of faculty time. Again, public expectations of high level technical expertise resulted in an educational revolution, this time in postgraduate training.

The consumer protection movement of the 1970's has been concerned with the issue of continuing professional competence. Politicians and other public spokesmen are focusing on assurance of professional quality extending throughout the lifetime of every practicing physician. In an era of rapidly expanding technological change, the question of currency in professional behavior is germane.

By the beginning of 1978 a total of 17 states had mandated continuing medical education requirements for relicensure of physicians, with other states moving in this direction. Medical societies of 15 states and the District of Columbia had also made continuing medical education a condition of membership.[1]

The United States Department of Health, Education, and Welfare is actively involved in the issue of professional competence. The Bureau of Health Manpower perceives the medical malpractice crisis as evidence of the public's dissatisfaction with present means of maintaining quality health care. In a recent monograph, the Bureau of Health Manpower explores possible pathways by which state and federal agencies might develop effective strategies to assure continuous excellence in professional performance.[2]

A recent article in THE WESTERN JOURNAL OF MEDICINE examined the present status of continuing medical education, and concluded with a call for research and development to further the state of the art.[3]

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Against the backdrop of public concern and some appropriate response practicing physicians—the object of this controvery—see the emergence of a multimillion dollar enterprise dedicated to improving them in the name of the public good. Each week most practicing physicians receive literally scores of educational brochures and public relations announcements that proclaim the benefits of attending particular programs. The sponsors of these offerings include local and state medical societies, colleges and academies of the medical specialties, university hospitals, communty hospitals, proprietary hospitals, chemical laboratories, independent medical school professors and some commercial self-appointed educational institutes. Courses cover the entire range of medical and biological sciences, but there is an obvious clustering of subjects believed to be particularly attractive to clinicians. The programs are usually offered on university campuses and in nearby hotels when sponsored by medical school departments. Other sponsoring agencies offer their courses at domestic and international recreational locations or on cruise ships, urging the potential attendee to combine his continuing education with vacation, making it all a tax deductible package.

It is estimated that more than 1.4 billion dollars is now spent (in terms of direct payment and physician time) on continuing education.[4] Researchers and entrepreneurs are developing and testing innovative technologies using programmed learning methods, audiovisual aids and computerized teaching programs. Continuing medical education is a reality that will, no doubt, have an impact on the professional life of each practicing physician within the next decade.

Out of this complex array of disorganized activity, some leadership must emerge. Goals and objectives must be defined and standards of educational quality must be set. American medical schools should, by rights, assume the responsibility because they traditionally have been the primary repository of medical research and teaching expertise. That their people have the skills and talents necessary has been shown clearly at the undergraduate and postgraduate (house officer) levels.

With this hypothesis in mind, what is the current status of continuing medical education in the medical schools throughout the United States? A questionnaire was sent to 113 deans of medical schools in December 1977. By March 1, 1978 there had been responses from 98 schools (87 percent). The questions and an analysis of the answers follow:

1. Do you have a department of continuing education?

All of the schools had some formal programs of continuing education, although they were ad-

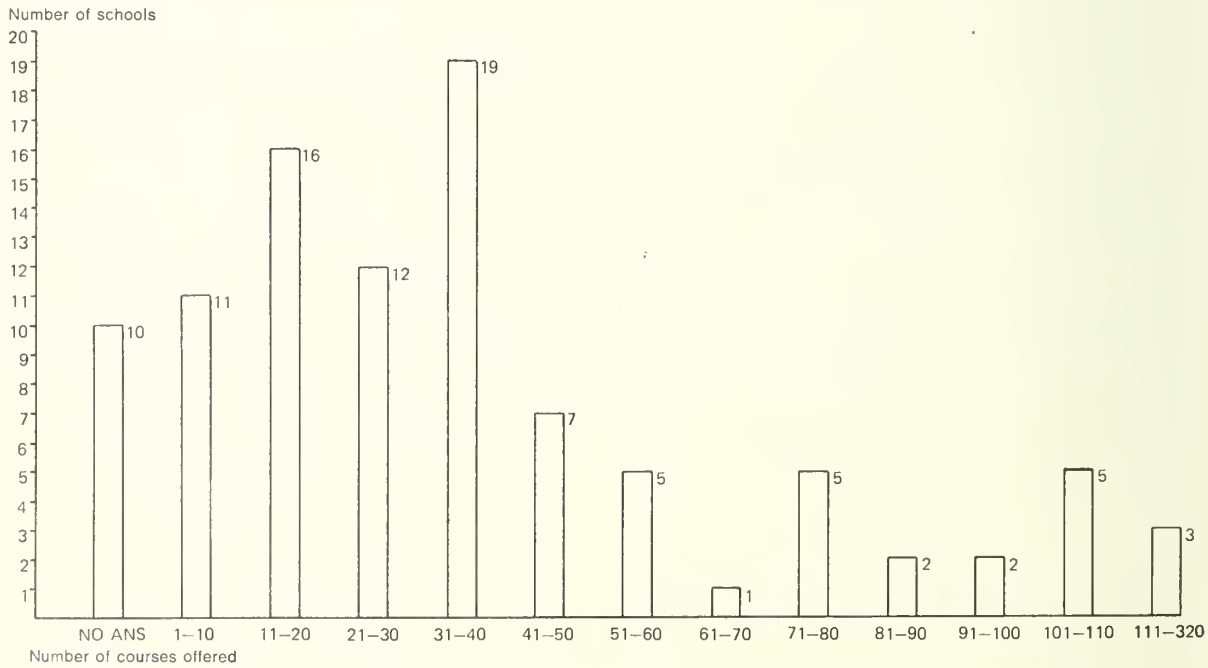

Figure 1.—Distribution of continuing medical education courses offered by American medical schools.

ministered differently—by a department, division, office, or the like.

2. Is the department of continuing education under the jurisdiction of the dean of the medical school? If not, under whose jurisdiction does it operate?

Interpretation of these answers was occasionally difficult because the organization tables of the schools vary widely. It seems, however, that the dean supervises this activity directly (or through an assistant dean), in 86 of the institutions that responded. A total of 12 departments of continuing medical education apparently operate somewhat more independently under a separate university organization such as a university extension.

3. Does the department of continuing education receive financial support from the medical school or university, or both?

Of the departments, 83 are funded to some extent by their institutions. The most common arrangement requires that support for programs be derived from attendance fees, but the schools supply the dollars for basic operating expenses. Fifteen respondents replied that they are on zero base budgeting, and must generate all their support money from attendance fees.

4. How many formal, didactic continuing medical education courses have you planned for the current academic year?

The range was extremely wide from 3 to 364 courses. Only eight schools, however, offered 100 or more courses (and they may have included informal, regular, in-house programs, such as grand rounds in this total). Most responses were in the 31- to 40-course range (see Figure 1) and the median was 35 courses.

5. Do you plan to expand your continuing education program next year?

Attesting to growing awareness of community needs in continuing medical education, 81 schools responded in the affirmative. Fourteen did not plan any increase in course offerings (of these two said that budgetary restrictions limited their operation). Two were not sure, and one failed to answer.

6. What do you charge for a class hour of education?

The answers were somewhat difficult to interpret because 11 schools did not respond and five gave vague replies, such as "varies." Eighty-two schools firmly stated a single average figure or a narrow range (for example, $5 to $10 or $10 to $15). Most were in the $5-to-$10 range with a median of $10 (see Figure 2).

7. What is the range of honoraria for an hour of presentation?

Twenty-eight schools do not pay full-time faculty for participation in continuing medical education because it is considered part of their teaching responsibility. One school distributed a percentage of the net income to the cooperating clinical departments that determine the use of excess funds. Six schools said that the honorarium not only includes the presentation, but also requires a full day of participation in the course (panels, workshops, and the like).

Interpreting the figures in terms of maximum honorarium, the peak of the curve is $150 (see Figure 3).

Nine schools pay as much as $500 for a guest speaker. One would assume that these speakers are exceptional, with national or international reputations.

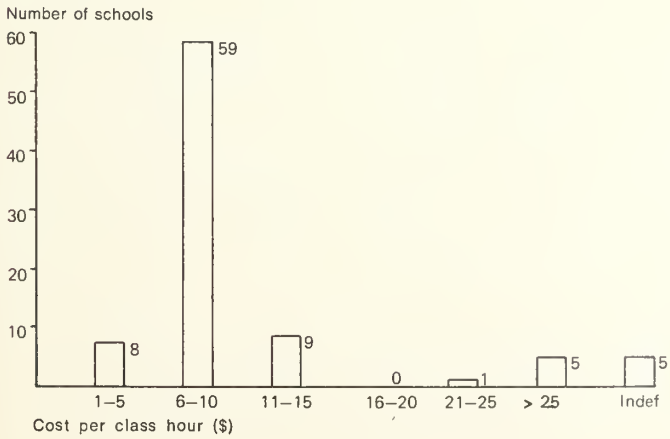

Figure 2.—Range of fees charged by American medical schools for continuing medical education.

8. Approximately what percentage of your courses are given on campus?

Three schools gave no continuing medical education courses on campus; one school stated that this was due to lack of adequate facilities which forced them to use hotels. Five schools replied that they gave all classes on campus. The median was 70 percent of programs offered at the medical school or university facility (see Figure 4). Four schools did not respond.

9. Do you give courses at vacation or recreational locations? Please state your opinions of this practice.

Forty-five deans replied *yes* and fifty-three replied *no*. Attitudes towards the practice tended to be negative, even among those who do give courses in recreational areas. Many schools condemned this practice.

Discussion

If medical schools are to provide greatly needed leadership in continuing medical education, as they provided in undergraduate instruction at the time of the Flexner Report, standards of quality in processes and content must be developed and a universal commitment to excellence will be required.

This study was designed to determine the current position of the medical schools regarding continuing medical education, which is being molded at present by many conflicting forces.

Our sampling seems to indicate that American

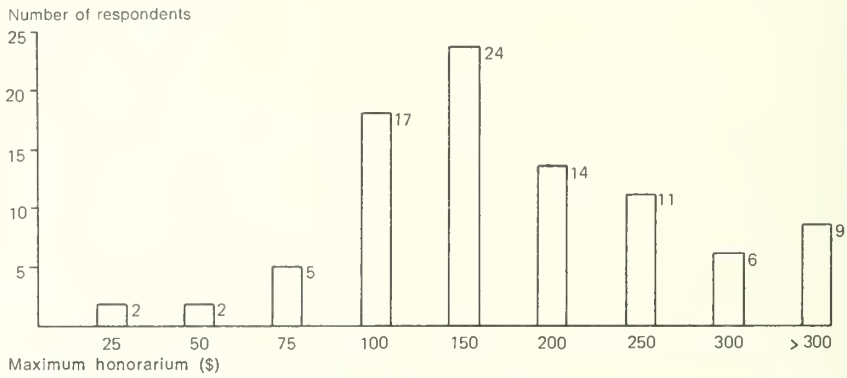

Figure 3.—Maximum honorarium paid to continuing medical education instructors.

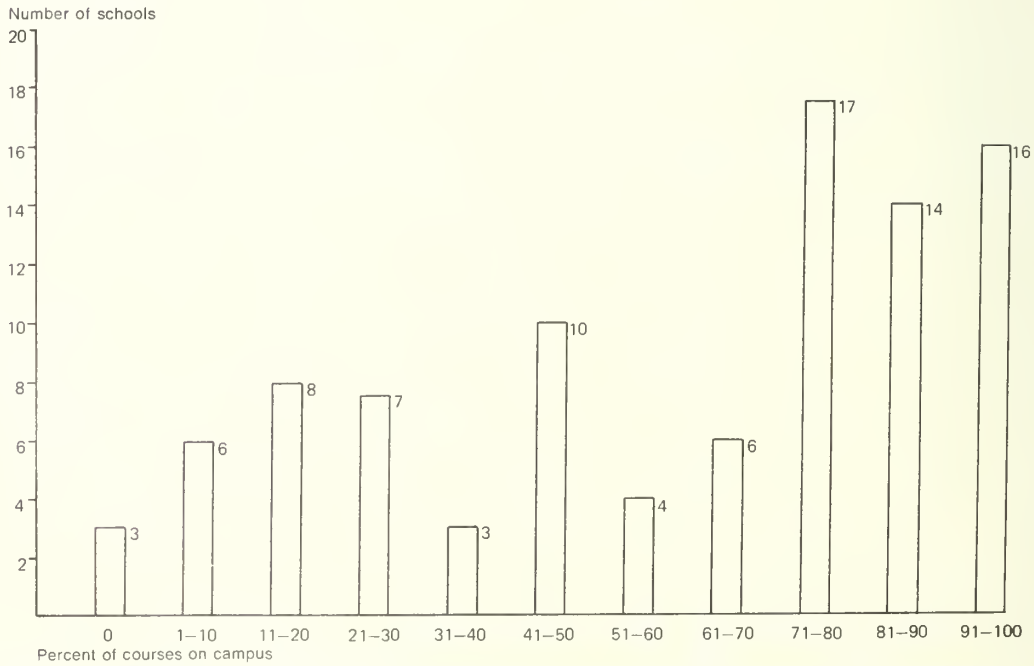

Figure 4.—Percentage of continuing medical education courses given on medical school campuses.

medical schools recognize the need for continuing medical education. The wide range in the number of courses offered, however, reflects indecision regarding proper levels of commitment. If the continuous education of practicing physicians is an academic responsibility, postgraduate medical schools would be a logical extension of undergraduate and house-officer training and the concept of a total postgraduate curriculum would follow.

Question 3 introduces the key issue of financing. As with undergraduate training, funding responsibility must ultimately be shared. In this free society, dominated by fee-for-service medicine, clinicians can certainly support the direct costs of each program. However, the infrastructure of institutions cannot be dependent on attendance fees if we are to move from programming trendy subjects to total curriculum development. A dependable stream of dollars is necessary for assuring quality and the widest possible assortment of opportunities. The divided focus of a continuing medical education program on zero based budgeting *must* result in academic compromise. Some responses to this question indicated that the institutional goal was to make continuing medical education totally self-supporting, which in this context seems counterproductive. Rather, schools should work together to develop a strategy to assure ongoing and dependable financing for continuing medical education.

Questions 6 and 7 may seem narrow, but they relate to broad issues critical to the viability of medical school programming. With the appearance of state requirements for professional reeducation, control and financing are problems for government licensing bodies. Within the medical establishment there are many agencies which consider themselves appropriate leaders in the development of continuing education. Among these, community hospitals and medical societies have been particularly vocal. Ultimately, however, these agencies, which are predominantly concerned with services for and care of patients, must turn to the vast resources of teaching and research talent of medical schools.

Two problems emerge. On one hand practicing physicians, unaccustomed to paying for ongoing education, are outraged by what they perceive as a special state-imposed financial burden mediated by the educating agency (for example, the medical school); and on the other hand, full-time medical school faculty members, already heavily burdened by undergraduate teaching, patient care and research responsibilities resent new demands that have little or no academic or financial reward. With the evolution and growth of continuing medical education, these conflicts must be resolved. At present, they can be burdensome to coordinators of active continuing medical education programs, particularly when planning the budget.

The final two questions shed light on the quandary planners face in finding a locale for their programs. The frequent use of off campus auditoriums reflects the low priority schools place on their commitment to community education. This commitment is a relatively new concept and one would hope that adequate on-campus facilities will become part of future plans.

Whether or not to use recreational sites generates considerable emotion. Both viewpoints can be convincingly argued. One question not asked, however, was "do you plan undergraduate programs in Tahiti?" The answers and conclusions seem obvious.

Summary

The current status of continuing medical education is reviewed. Results from questionnaires sent to deans of American medical schools are given. Issues involved in the development of the questionnaire and generated by the answers are discussed.

REFERENCES

1. Continuing Medical Education Fact Sheet. American Medical Association, Apr 1, 1977

2. Competence in the Medical Professions: A Strategy. DHEW Publication No (HRA) 77-35. Health Resources Administration, 1977, pp 1-8

3. Manning PR: Continuing medical education in midpassage. West J Med 128:260-265, Mar 1978

4. Miller LA: The current investment in Continuing Medical Education, chap 14, *In* Egdall RH, Gertman PM (Eds): Quality Health Care. Germantown, MD, Aspen Systems Corp, 1977, pp 143-160

Refer to: Phillips LA: Skull radiography and professional liability (Information). West J Med 131:82-83, Jul 1979

Information

Skull Radiography and Professional Liability

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IT IS WIDELY ASSUMED by emergency physicians that skull roentgenograms provide a measure of protection against malpractice actions. This belief is at least partly responsible for the 6 to 8 million radiographic examinations of the skull done every year, which cost an average of $50 each.

The following two cases suggest that allowing normal findings on x-ray films of the skull to influence clinical decisions is perhaps more dangerous than failing to request skull radiography.

Reports of Cases

CASE 1. An 11-year-old boy was injured in a schoolyard fight. He was taken to hospital where radiographic examination of the boy's skull was carried out and he was seen by at least two resident physicians and an attending physician. No abnormalities were noted on the x-ray films of the skull and a complete clinical evaluation was not made, no provision was made for further careful observation and no head trauma instruction sheet was given to the boy's father.

Approximately two hours after release the boy was brought back to the hospital by his father. Another physician immediately recognized an epidural hematoma and contacted a neurosurgeon, who responded belatedly due to an automobile accident en route to the hospital. An epidural hematoma was removed too late to prevent quadriplegia with aphasia. A skull fracture was identified at operation and a record $4,025,000 award was made in the professional liability suit that followed.[1,2]

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CASE 2. A 24-year-old man came into the emergency facility at a university hospital. He said that he had been struck above the right ear by the tip of an umbrella which had been thrown at him. The umbrella had stuck in his head and it was necessary for his brother to pull it out.

The patient was seen by two physicians, one a neurosurgical resident. Both noted a 1 cm laceration above the right ear and some numbness over the nose, upper lip and roof of the mouth. Good quality x-ray films of the skull were made and interpreted as normal. The chief neurosurgical resident was telephoned and he advised having the patient return to the clinic nine days later.

On the following day the patient visited the outpatient department of another hospital. A physician there, impressed with the man's story, ordered additional x-ray studies and tomography, which showed fragments of bone about 2 cm inside the skull. Craniotomy was carried out and the fragments were removed.

After release from hospital the man consulted an attorney about bringing suit against the university hospital. Apparently he was advised against legal action because there was no physical impairment or permanent damage.

Discussion

In both cases x-ray films of the skull showed no abnormalities, and for this reason careful clinical evaluation and observation were neglected. Searches of the medical and legal literature, and information from professional liability insurers, have suggested that physicians are much more likely to be sued for missing a fracture on x-ray films of the skull than for not requesting the films.[3,4] As a matter of fact, the author has been unable to document a single case in which a physician was sued for malpractice for not obtaining x-ray films of the skull after careful clinical evaluation and observation.

During the past several years we have reviewed all skull roentgenograms requested from the emergency facility of the University of Washington Hospital, and have completed two projects for the Bureau of Radiological Health and the Washington State Professional Standards Review Organization involving the evaluation of more than 3,600 skull radiographic examinations done at Harborview Medical Center.[5,6] Results of these studies have suggested that at least 80 percent of all emergency facility skull radiography is un-

necessary or misleading and probably increases malpractice jeopardy because of inevitable false negative reports. Skull radiography simply does not rule out skull fracture or brain damage.

Our recommendation for the faculty of the University Hospital emergency facility is that no x-ray films of the skull be made immediately when patients present with head trauma. If after careful clinical evaluation and observation one of the following "high yield criteria" is present, cranial computerized tomography should be requested:

- Unconsciousness (including cases of alcoholic patients who cannot be aroused) or a documented decreasing level of consciousness at the time of arrival at the emergency facility after metabolic and seizure disorders are excluded as the cause of unconsciousness.
- Skull depression palpable or identified by probe through laceration or puncture wound.
- Unexplained focal neurological signs.

Skull radiography should be requested only when indicated to confirm findings from computerized tomography.

REFERENCES

1. Martin M: That record malpractice award—Why $4,025,000? Med Economics, Jul 23, 1973, pp 120-148
2. Niles vs Mt. Zion Hospital and the City of San Rafael. 42 Cal App 3 ed, 116 Cal Rptr 733, 1974
3. Summary of Malpractice Closed Claims. National Association of Insurance Commissioners (Milwaukee, WI) Vol 1: No 4, May 1977
4. Malpractice Digest. Sep/Oct 1978, p 5
5. Phillips LA: A Study of the Effect of High Yield Criteria for Emergency Room Skull Radiography, DHEW Publication No. 78-8069. US Dept of Health, Education, and Welfare, FDA, Jul 1978
6. Phillips LA: Emergency Facility Skull Radiography. Report submitted to DHEW/Public Health Service, Bureau of Radiological Health and Health Care Financing Administration (Washington State PSRO), Aug 1978

Refer to: Southern Medical Association meeting in Las Vegas (Information). West J Med 131:83, Jul 1979

Information

Southern Medical Association Meeting in Las Vegas

FOR THE FIRST TIME the American Medical Association's Council on Continuing Physician Education will be presenting a series of 22 postgraduate courses in conjunction with the Southern Medical Association at its annual Scientific Assembly, November 4 through 7, 1979, in Las Vegas. The courses as well as the total scientific program are planned to offer a variety of subjects for all major specialties.

The Southern Medical Association presents an outstanding convention with 21 section programs in the various specialties, more than 200 exhibits, social and educational events for spouses, a president's reception and dance, and other activities. This is the first assembly that the Southern Medical Association has planned outside the southeastern area.

Physicians may request literature on the courses from the AMA Department of Meeting Services, 535 North Dearborn Street, Chicago, IL 60610, or on the total convention from the Southern Medical Association, 2601 Highland Avenue, Birmingham, AL 35205.

in memoriam

Bell, Dudley Philip, Oakland. Died May 5, 1979 in Hawaii, aged 71. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1933. Licensed in California in 1934. Dr. Bell was a retired member of the Alameda-Contra Costa Medical Association.

Bolze, Edward, jr., San Francisco. Died April 20, 1979, aged 83. Graduate of the University of California Medical School, Berkeley-San Francisco, 1925. Licensed in California in 1925. Dr. Bolze was a retired member of the San Francisco Medical Society.

Campbell, Dwight G., Paramount. Died March 3, 1979, aged 57. Graduate of Ohio State University College of Medicine, Columbus, 1952. Licensed in California in 1953. Dr. Campbell was a member of the Los Angeles County Medical Association.

Carroll, Kevin J., Laguna Beach. Died July 14, 1978 of heart disease, aged 78. Graduate of the College of Physicians and Surgeons, Los Angeles, 1941. Licensed in California in 1941. MD degree from California College of Medicine, 1962. Dr. Carroll was a retired member of the Orange County Medical Association.

Coker, John Kenner, jr., Bakersfield. Died April 6, 1979 in Monterey of cancer, aged 71. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1934. Licensed in California in 1944. Dr. Coker was a retired member of the Kern County Medical Society.

Ermshar, Lloyd G., Coronado. Died November 4, 1978 of pulmonary embolism, aged 68. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1937. Licensed in California in 1937. Dr. Ermshar was a retired member of the Los Angeles County Medical Association.

Faber, Harold Kniest, San Francisco. Died April 27, 1979 in San Francisco, aged 94. Graduate of the University of Michigan Medical School, Ann Arbor, 1911. Licensed in California in 1916. Dr. Faber was a retired member of the San Francisco Medical Society.

Johnson, Helen M., Salinas. Died April 14, 1979 in Salinas, aged 75. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1930. Licensed in California in 1930. Dr. Johnson was a member of the Monterey County Medical Society.

Krummes, Harry P., Concord. Died April 26, 1979 in Oakland, aged 89. Graduate of Hahnemann Medical College of the Pacific, San Francisco, 1913. Licensed in California in 1915. Dr. Krummes was a retired member of the Alameda-Contra Costa Medical Association.

Marlow, Arthur Ashley, La Jolla. Died April 23, 1979, aged 76. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1929. Licensed in California in 1936. Dr. Marlow was a member of the San Diego County Medical Society.

Porter, James Llewellyn, Sacramento. Died April 1, 1979 in Santa Cruz of heart disease, aged 65. Graduate of the University of Southern California School of Medicine, Los Angeles, 1940. Licensed in California in 1940. Dr. Porter was a retired member of the Sacramento County Medical Society.

Porter, John E., La Mesa. Died April 24, 1979 in San Diego, aged 87. Graduate of the Medical College of Virginia, Richmond, 1915. Licensed in California in 1937. Dr. Porter was a retired member of the San Diego County Medical Society.

Schmidt, Otto Ernest Lincoln, San Mateo. Died April 28, 1979 in San Mateo of heart disease, aged 67. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1939. Licensed in California in 1942. Dr. Schmidt was a member of the San Mateo County Medical Society.

Trolan, J. Austin, Concord. Died May 16, 1979 of heart disease, aged 70. Graduate of the University of California Medical School, Berkeley-San Francisco, 1933. Licensed in California in 1934. Dr. Trolan was a retired member of the Alameda-Contra Costa Medical Association.

Wells, John J., San Jose. Died December 15, 1978 of esophageal hemorrhage, aged 74. Graduate of Harvard Medical School, Boston, 1931. Licensed in California in 1955. Dr. Wells was a retired member of the Santa Clara County Medical Society.

Wilcox, Alfred, Santa Barbara. Died May 5, 1979 in Santa Barbara, aged 79. Graduate of the University of Colorado School of Medicine, Denver, 1927. Licensed in California in 1929. Dr. Wilcox was a retired member of the Medical Society of Santa Barbara County.

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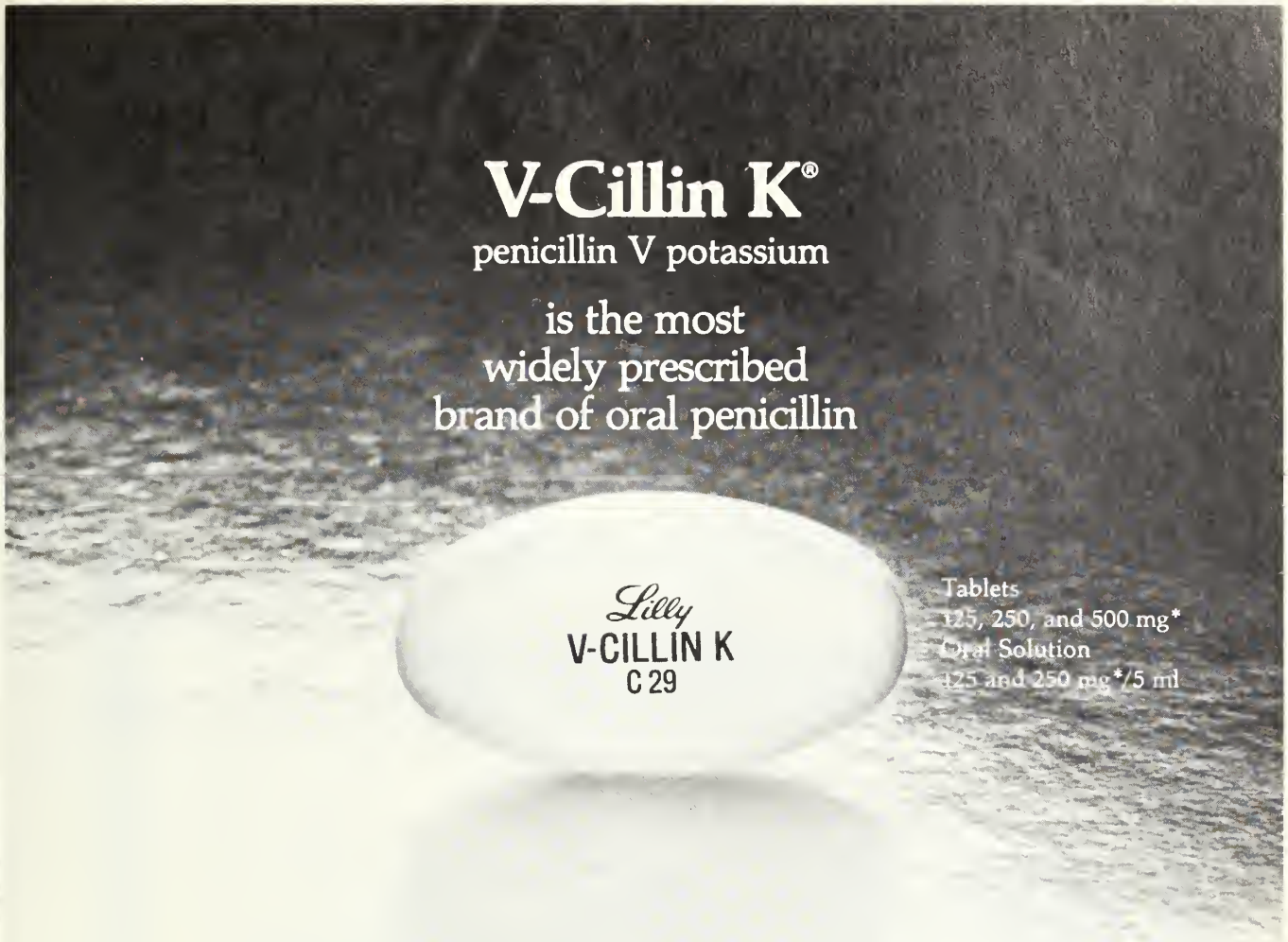

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ANESTHESIOLOGY

August 4—**Obstetrical Anesthesia.** Mercy Hospital and Medical Center, San Diego. Saturday. Contact: Gilbert E. Kinyon, MD, Dir. of Anesthesia, Mercy Hospital & Medical Center, 4077 Fifth Ave., San Diego 92103. (714) 294-8037.

August 18—**Current Concepts in Anesthesia.** Kaiser-Permanente at Red Lion Inn, Sacramento. Saturday. 6 hrs. Contact: B. L. Vandermeer, MD, Chief of Anesthesia, Kaiser Foundation Hosp., 2025 Morse Ave., Sacramento 95825. (916) 486-5011.

September 15-22—**Practical Management of Anesthetic Problems.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 31½ hrs. $325.

October 20-24—**American Society of Anesthesiologists—Annual Meeting.** San Francisco. Saturday-Wednesday. Contact: William S. Marinko, Asst. Exec. Sec., ASA, 515 Busse Highway, Park Ridge, IL 60068. (312) 825-5586.

October 25-November 2—**Post ASA Hawaiian Seminar.** Kona Village Resort, Hawaii. 9 days. 28 hrs. Contact: Adham Safwat, Box 7550, Menlo Park 94025. (415) 494-3799.

October 26-28—**Clinical Anesthesia Monitoring.** Anesthesiology Educational Foundation and Calif. Soc. of Anesthesiologists at Holiday Inn, Monterey. Friday-Sunday. Contact: AEF, P.O. Box 24230, Federal Bldg., Los Angeles 90024.

CANCER

August 1-5—**20th Annual Advanced Seminars in Dermatology (Current Topics in Cancer)—Malignant Melanoma and Lymphoma.** See Medicine, August 1-5.

September 15—**Histopathology of Head and Neck Tumors.** Head and Neck Cancer Network of the No. Calif. Cancer Program and San Francisco Regional Cancer Foundation at Children's Hospital, San Francisco. Saturday. 8 hrs. Contact: SF Regional Cancer Fnd., 14th and Lake, San Francisco 94118. (415) 221-2132.

September 15-16—**Advances in the Cause, Detection and Prevention of Cancer: A Multi-Disciplinary Analysis.** UCSF at Sheraton-Palace, San Francisco. Saturday-Sunday.

September 20-22—**Bladder Cancer.** American Urological Assn. at Hilton Hotel, San Diego. Thursday-Saturday. 16 hrs. $200, members; $250, nonmembers. Contact: Mary Rohan, AUA Office of Education, P.O. Box 1129, Aspen, CO 81611. (303) 925-2012.

September 26—**Head and Neck Cancer Symposium.** Hospital of the Good Samaritan, Los Angeles. Wednesday. 7 hrs. Contact: Janie Sternal, CME Coordinator, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

October 20—**New Methods for Fighting Cancer.** San Francisco Regional Cancer Foundation at Fireman's Fund Building, San Francisco. Saturday. 4 hrs. Contact: Dr. Terry Sheehy, S.F. Regional Cancer Foundation, 14th and Lake, San Francisco 94118. (415) 221-2132.

November 9-10—**Gynecologic and Breast Cancer: Current Concepts and Controversies.** Mt. Zion Hospital and Medical Center at Fairmont Hotel, San Francisco. Friday-Saturday. Contact: Office of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

EMERGENCY MEDICINE

August 13-17—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 43 hrs. $350.

September 8—**Orange County Emergency Workshop Part III—Neurological Trauma.** UCI. Saturday. 5 hrs.

September 17-21—**Topics in Emergency Medicine.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Monday-Friday. 40 hrs. $325.

September 24—**Trauma—Auto and Motorcycle Patients.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

September 24-28—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Monday-Friday. 43 hrs. $350.

October 8-12—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 43 hrs. $350.

December 6-8—**Trauma.** See Surgery, December 6-8.

December 10-14—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 43 hrs. $350.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

MEDICINE

July 19-20—**New Approaches to Immunosuppression.** PMC at Fairmont Hotel, San Francisco. Thursday-Friday. 12 hrs. $100.

July 23—**Management of Diabetes.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

July 23-24—**Microcirculatory Approach to Current Medical and Surgical Problems.** Microcirculatory Society and American Heart Assn., Greater Los Angeles Affiliate, at Hilton, San Diego. Monday-Tuesday. 14 hrs. $175, before April 1; $200, thereafter. Contact: Nomi Feldman, Conf. Coordinator, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

July 27-29—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Sunday. 15 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

July 27-30—**Medical Mycology-Dermatomycology—4th Annual Course.** Memorial Hospital Medical Center-UCI Center for Health Education at Sheraton-Newport, Newport Beach. Friday-Monday. 36 hrs. $300. Contact: Prog. Coord., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

July 30-August 3—**Endocrinology and Metabolism.** UCSF at Hyatt Regency, San Francisco. Monday-Friday.

August 1-5—**20th Annual Seminars in Dermatology (Current Topics in Cancer)—Malignant Melanoma and Lymphoma.** Memorial Hosp. Med. Ctr.-UCI Ctr. for Health Education at Sheraton-Newport, Newport Beach. 14 hrs. $175. Contact: Prog. Coord., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 4—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

August 16-18—**Podiatric Dermatology Symposium.** STAN. Thursday-Saturday. 17 hrs. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

August 27-31—**Update in Internal Medicine.** Mills Memorial Hospital at Golden Gateway Holiday Inn, San Francisco. Monday-Friday. 32 hrs. $200. Contact: Robert Siegel, MD, Med. Staff Office, Mills Memorial Hosp., 100 S. San Mateo Dr., 94401. (415) 342-5667.

August 29-31—**Skin Microbiology: Relevance to Clinical Infection.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday. 18 hrs. $190.

September 9-14—**Non-Invasive Diagnostic Technique in Vascular Disease.** UCSD at Sheraton Harbor Island Hotel, San Diego. Sunday-Friday. 35 hrs. $300.

September 10-13—**Electrocardiography: Core Curriculum and Self-Assessment.** American College of Cardiology at Fairmont Hotel, San Francisco. Monday-Thursday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

September 16-20—**Pacific Dermatologic Association—Annual Meeting.** Hyatt Regency, San Francisco. Sunday-Thursday. 15½ hrs. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno NV 89509. (702) 323-2461.

September 24-28—**An Advanced Course for Internists.** STAN at San Francisco. Monday-Friday.

September 24-28—**Vascular Medicine and Surgery.** STAN at Stanford Court, San Francisco. Monday-Friday. 25 hrs. $290.

September 28-30—**Coronary Disease, Exercise Testing and Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton on the Wharf, San Francisco. Friday-Sunday. 13 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

October 3-4—**47th Annual Fall Symposium and 12th George C. Griffith Scientific Lecture.** American Heart Assn., Greater Los Angeles Affiliate, at Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hrs. $85, member any Heart Assn.; $110, nonmember. Contact: Alexis Krieger, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

October 8—**Calcium Metabolism.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

October 11-12—**49th Annual Physicians' Postgraduate Symposium on Cardiovascular Disease.** American Heart Assn., San Francisco Chapter, at San Franciscan Hotel, San Francisco. Thursday-Friday. Contact: Patty MacJennett, AHA, 421 Powell St., San Francisco 94108. (415) 433-2273, ext. 443.

October 15-19—**Advanced Course for Internists.** STAN at Hyatt on Union Square, San Francisco. Monday-Friday. 25 hrs. $290.

October 18-20—**Cardiology Update—1979.** American College of Cardiology at Del Monte Hyatt, Monterey. Saturday-Monday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

October 18-21—**Society of Nuclear Medicine—4th Annual Western Regional Meeting.** Monterey Conference Center, Monterey. Thursday-Sunday. Contact: Justine Parker, Western Regional Chapters, Society of Nuclear Medicine, P.O. Box 40279, San Francisco 94140. (415) 647-0722.

October 19-20—**Mycology Review** (a course for residents in dermatology and pathology). STAN. Friday-Saturday. 16 hrs. $50 per day; $25 per day for residents and trainees. Contact: Paul H. Jacobs, MD, Dept. of Derm., Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

October 20-27—**British Clinical Cardiology in the Paul Wood Tradition.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $325.

October 22—**Respiratory Diseases Due to Pollutants.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

November 2-3—**California Society of Internal Medicine—Annual Meeting.** Hotel del Coronado, Coronado. Friday-Saturday. Contact: CSIM, 703 Market St., 1412 Central Tower, San Francisco 94103. (415) 362-1548.

November 3—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Sch. of Med., Stanford 94305. (415) 497-6101.

November 4-6—**Fifth Annual Workshop on the Thyroid.** American Thyroid Assn. at Golden Gateway Holiday Inn, San Francisco. Sunday-Tuesday. 14 hrs. $200. Contact: Dr. Lewis Braverman, Univ. of Mass. Med. Ctr., 55 Lake Ave., N., Worchester, MA 01605.

November 5-14—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

November 8-10—**Coronary Artery Disease: Medical and Surgical Decisions.** Eisenhower Medical Center at Marriott Las Palmas Resort, Rancho Mirage. Thursday-Saturday. Contact: John J. Deller, MD, Dir. of Ed. and Research, Eisenhower Med. Ctr., 39000 Bob Hope Dr., Palm Desert 92260. (714) 346-3911.

November 10—**Viral Diseases in Clinical Practices.** Alta Bates Hospital, Berkeley. Saturday. 6 hrs. Contact: Claudia Read, Med. Ed., Alta Bates Hosp., 3001 Colby St., Berkeley 94705. (415) 845-7110, ext. 2055.

November 10-11—**Practical Nephrology for the Primary Care Physician.** UCLA. Saturday-Sunday.

November 15-16—**Neurology Update.** UCSD at Vacation Village, San Diego. Thursday-Friday.

November 29-December 1—**Infectious Disease Conference.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday.

December 1-2—**Practical Endocrinology for Primary Care Physicians.** UCLA. Saturday-Sunday.

December 7-8—**Allergy/Immunology, Infectious Diseases, Endocrinology/Metabolism, Oncology.** American College of Physicians at San Francisco. Friday-Saturday. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200.

December 7-9—**Advances in Heart Disease 1980—12th Annual Seminar on Clinical Cardiology.** American College of Cardiology at Fairmont Hotel, San Francisco. Friday-Sunday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

OBSTETRICS AND GYNECOLOGY

August 6-12—**Reproductive Endocrinology, Infertility and Contraception.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 24½ hrs. $300.

August 25-31—**Edward Tyler Symposium on the Practical Management of the Infertile Couple—3rd Annual.** Tyler Medical Clinic, Los Angeles, and Univ. of Hawaii School of Medicine at Maui Surf Hotel, Maui, Hawaii. One week. 16 hrs. $200. Contact: Jetset Tours, 2029 Century Park East, Suite 2130, Los Angeles 90067.

November 5-8—**Perinatal Medicine: State of the Art—1979.** UCSD at Vacation Village, San Diego. Monday-Thursday.

November 9-11—**Peripartum Period.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Friday-Sunday. 6 hrs. $150. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 29-December 1—**High-Risk Pregnancy—3rd Annual Conference.** Memorial Hospital Medical Center-UCI Center for Health Education at Canyon Hotel, Palm Springs. Thursday-Saturday. 18 hrs. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 6-8—**Gynecologic Urology: Theory and Practice, Basic and Advanced.** Memorial Hospital Medical Center-UCI Center for Health Education at Sheraton-Universal, Hollywood. Thursday-Saturday. 20 hrs. $300. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

PEDIATRICS

July 28—**The Child's Hip: A Program for the Primary Care Physician.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7 hrs.

August 4—**Pediatric Dermatology Seminar.** See Medicine, August 4.

September 19-20—**36th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Hilton Hotel, Los Angeles. Wednesday-Thursday. Contact: LAPS, P.O. Box 2022, Inglewood 90305.

October 13-18—**American Academy of Pediatrics—Annual Meeting.** Hilton Hotel and Brooks Hall, San Francisco. One week. 33-36 hrs. $60, members; $120, nonmembers. Contact: W. G. Janzen, Meeting Mgr., AAP, 1801 Hinman Ave., Evanston, IL 60204. (312) 869-4255.

November 12-14—**Primary Care Pediatrics.** UCI at Marriott Inn, Newport Beach. Monday-Wednesday. 17 hrs.

November 16-19—**Las Vegas Seminars.** American Academy of Pediatrics, Calif. Chapters 1, 2, 3, at Hilton Hotel, Las Vegas. Friday-Monday. $175, members; $200, nonmembers. Contact: AAP, Chap. 2, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

November 26-30—**Developmentally Disabled Child.** UCSD at Vacation Village, San Diego. Monday-Friday.

PSYCHIATRY

July 21-22—**Medical Aspects of Psychiatric Practice.** UCLA. Saturday-Sunday. 9 hrs. $150.

July 23-27—**Family Interactional Psychotherapy: Process and Practices.** Mental Research Institute, Palo Alto. Monday-Friday. 17 hrs. $140. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

July 28—**Introduction to Human Systems and Communication—The Interactional View.** Mental Research Institute, Palo Alto. Saturday. 7 hrs. $75. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

July 30-August 1—**Hypnotherapy: Bases and Applications.** Mental Research Institute, Palo Alto. Monday-Wednesday. 6 hrs. $50. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

July 30-August 2—**Brief Therapy.** Mental Research Institute, Palo Alto. Monday-Thursday. 15 hrs. $140. Contact: MRI, 555 Middlefield Rd., Palto Alto 94301. (415) 321-3055.

August 3-4—**Present Imperfect: Reflections of Family Therapists, 1959-1979-1999—4th Don D. Jackson Memorial Conference.** Mental Research Institute at Sheraton-Palace, San Francisco. Friday-Saturday. 12 hrs. $135. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

August 6—**Introduction to Human Systems and Communication—The Interactional View.** Mental Research Institute, Palo Alto. Monday. 7 hrs. $75. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

August 6-9—**Family Crises: Intervention Strategies.** Mental Research Institute, Palo Alto. Monday-Thursday. 12 hrs. $100. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

August 11—**Community Treatment of Schizophrenia.** Mental Research Institute, Palo Alto. Saturday. 5 hrs. $60. Conact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

September 10—**Ambulatory Treatment of the Depressed Patient.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

September 15—**Psychopharmacology in Clinical Practice: A Practicum in Mind-Allergy Drugs.** UCLA. Saturday.

October 12-14—**Infant Psychiatry II.** UCSF. Friday-Sunday.

October 13—**Explorations of Healing in Psychotherapy.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 6 hrs. $60.

October 27—**Psychiatry Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 7 hrs. Contact: Prog. Coordinator, UCI Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 28-31—**Academy of Psychosomatic Medicine—Annual Meeting.** Fairmont Hotel, San Francisco. Sunday-Wednesday. Contact: Thomas C. Nelson, Exec. Dir., 70 W. Hubbard, Suite 202, Chicago, IL 60610. (312) 644-2623.

RADIOLOGY AND PATHOLOGY

July 28-August 4—**Medical Imaging.** American College of Medical Imaging at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

September 13-May 8—**L.A. Bone and Joint Clinico-Pathological-Radiological Correlation and Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. 2nd Thursday of each month. 3 hrs./session. Contact: Prog. Coord., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 80801. (213) 595-3811.

October 13-21—**International Body Imaging Conference—4th Annual.** West Park Hospital, Canoga Park, at Royal Lahaina Hotel, Maui, Hawaii. 9 days. 30 hrs. $295. Contact: Conf. Sec., Imaging Conf., West Park Hosp., Dept. of Radiology, 22141 Roscoe Blvd., Canoga Park 91304.

October 18-21—**Society of Nuclear Medicine—4th Annual Western Regional Meeting.** See Medicine, October 18-21.

October 19-20—**Mycology Review** (a course for residents in dermatology and pathology). See Medicine, October 19-20.

November 2-4—**Radiology of the Gastrointestinal System (II).** American College of Radiology at San Francisco. Friday-Sunday. 15 hrs. $275. Contact: Maurice H. Trautz, Dir. of Ed., ACR, 6900 Wisconsin Ave., Chevy Chase, MD 20015. (301) 654-6900.

November 3-4—**Leo G. Rigler Radiology Course.** UCLA at Biltmore Hotel, Los Angeles. Saturday-Sunday.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 23 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

July 23-24—**Microcirculatory Approach to Current Medical and Surgical Problems.** See Medicine, July 23-24.

August 4-11—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 28 hrs. $325.

August 20—**Fluid-Electrolyte Problems in the Surgical Patient.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

September 24—**Trauma—Auto and Motorcycle Patients.** See Emergency Medicine, September 24.

September 24-28—**Vascular Medicine and Surgery.** See Medicine, September 24-28.

October 4-6—**Advances and Controversies in Vascular Surgery.** Cedars-Sinai Medical Center at Century Plaza Hotel, Los Angeles. Thursday-Saturday. 19 hrs. $195. Contact: Lore Kahane, Room 2049, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles 90048. (213) 855-5547.

October 6—**Update of Pediatric Opthalmology.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $85. Contact: Lu Hendricks, Jules Stein Eye Inst., UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

October 11-13—**Surface Replacement.** UCLA. Thursday-Saturday.

October 19-20—**Cataract Surgery Pragmatics.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 14 hrs. $150. Contact: Program Coordinator. Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 585-3811.

October 28-November 9—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200, otolaryngologists; $900, residents. Contact: Antonio De La Cruz, MD, Ear Research Inst., 256 S. Lake St., Los Angeles 90057.

November 5-9—**American Academy of Ophthalmology.** Civic Auditorium, San Francisco. Monday-Friday. Contact: Faye Anderson, Dir. of Mtgs., P.O. Box 7424, San Francisco 94120. (415) 563-5725.

November 24-December 1—**International Seminar on Operative Arthroscopy.** UCLA. One week. 39 hrs. $650, with laboratories; $450, without laboratories.

December 6-8—**Trauma.** No. Calif. Chap. Committee on Trauma of the American College of Surgeons at Claremont Resort Hotel, Oakland. Thursday-Saturday. Contact: F. William Blaisdell, MD, Dept. of Surg., UCD Sch. of Med., Rm. 257, 4301 X St., Sacramento 95817. (916) 453-2207.

December 6-8—**Gynecologic Urology.** See Obstetrics and Gynecology, December 6-8.

December 8—**Blepharoplasty and Other Cosmetic Surgery of the Eyelid.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

OF INTEREST TO ALL PHYSICIANS

July 19-21—**Tissue Fluid Pressure and Composition.** UCSD. Thursday-Saturday. 17 hrs. $190.

August 4-11—**Hypnosis and Imagery: Practical Applications.** Bay General Community Hosp., Chula Vista, at Hotel Intercontinental, Maui, Hawaii. One week. 15 hrs. $150. Contact: Errol R. Korn, MD, 480 4th Ave., Suite 409, Chula Vista 92010. (714) 420-8051.

August 6—**The Seductive Patient.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

August 11-22—**Postgraduate Refresher Course—22nd Annual.** USC at Honolulu and Maui or Kauai, Hawaii. Two weeks. 39 hrs. $325.

August 19-24—**Family Practice Refresher Course—7th Annual.** UCD at Del Monte Hyatt, Monterey. One week. 30 hrs. $225.

August 25-31—**Edward Tyler Symposium on the Practical Management of the Infertile Couple—3rd Annual.** See Obstetrics and Gynecology, August 25-31.

August 28-October 16—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. Tuesdays; 8-10 p.m.

September 1-8—**Manipulation, Mobilization and Related Techniques in the Treatment of Musculo-Skeletal and Myofascial Pain Syndromes.** USC at Sheraton Waikiki Hotel, Hawaii. One week. 27½ hrs. $325.

September 9-13—**American Academy for Cerebral Palsy and Developmental Medicine—Annual Meeting.** St. Francis Hotel, San Francisco. Sunday-Thursday. 26 hrs. $95. Contact: Helen Bryan, Assoc. Exec. Dir., 1255 New Hampshire Ave. NW, #1030, Washington, DC 20036. (202) 659-8251.

September 13-14—**Long Term Care Programs for the Elderly.** UCLA at Biltmore Hotel, Los Angeles. Thursday-Friday.

September 14-15—**The Last Horizon: Practical Solutions to Improved Patient Care of Patients with Terminal Illness.** UCD at Mansion Inn, Sacramento. Friday-Saturday. 15 hrs.

September 14-16—**Holistic Medicine.** Psychosomatic Medicine Clinic, Berkeley; American Holistic Medical Assn.; Symposia Medicus, Walnut Creek, at Biltmore Hotel, Santa Barbara. Friday-Sunday. 12 hrs. $185. Contact: Symposia Medicus, 2815 Mitchell Dr., No. 116, Walnut Creek 94598. (415) 935-7889.

September 15—**Psychopharmacology in Clinical Practice: A Practicum in Mind-Allergy Drugs.** See Psychiatry, September 15.

September 20—**California Venereal Disease Controllers' Clinical Session.** CMA Task Force on Venereal Disease, Calif. VD Controllers Assn. and Calif. Academy of Preventive Medicine at San Mateo. Thursday. Contact: Karin McGhee, CMA.

October 11-13—**Western Occupational Medical Association.** Monterey. Thursday-Saturday. Contact: B. H. Bravinder, P.O. Box 201, Alamo 94507.

October 13-21—**International Body Imaging Conference—4th Annual.** West Park Hospital at Royal Lahaina Hotel, Maui, Hawaii. 9 days. 30 hrs. $295. Contact: Conference Sec., Imaging Conf., West Park Hospital, Dept. of Radiology, 22141 Roscoe Blvd., Canoga Park 91304.

October 14-15—**Advances in Alcoholism Symposium.** UCSD and Raleigh Hills Foundation at Newporter Inn, Newport Beach. Sunday-Monday. 14 hrs. $150. Contact: Robert E. Schmitz, MD, Raleigh Hills Fnd., 881 Dover Dr., No. 20, Newport Beach 92663. (714) 645-4310.

October 20—**Exercise Medicine.** UCLA. Saturday.

October 28-31—**California Academy of Family Physicians—Annual Scientific Assembly.** Masonic Auditorium, San Francisco. Sunday-Wednesday. Contact: CAFP, 9 First St., San Francisco 94105. (415) 982-6091.

November 4-7—**Southern Medical Association.** MGM Grand Hotel, Las Vegas. Sunday-Wednesday. In addition to 21 SMA programs, 22 postgraduate courses presented by AMA's Council on Cont. Physician Ed. Contact: SMA, 2601 Highland Ave., Birmingham, AL 35205.

November 5-9—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $290.

November 12-17—**American Society of Clinical Hypnosis—22nd Annual Scientific Meeting and Workshops.** San Francisco. Monday-Saturday. 40 hrs. $75, scientific program; $250, workshops. Contact: William F. Hoffman, Jr., Exec. Dir., 2400 E. Devon Ave., Suite 218, Des Plaines, IL 60018.

November 26-30—**Postgraduate Institute for Primary Care Physicians.** UCSD at Hilton Hotel, San Diego. Monday-Friday. 40 hrs.

November 30—**The Many Faces of Shock—1979.** Daniel Freeman Hospital at Hyatt House, Los Angeles. Friday. 6 hrs. $90. Contact: Donald A. Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Hosp., 333 N. Prairie Ave., Inglewood 90301. (213) 674-7050.

December 5-7—**Prevention in Primary Care.** UCSD at Vacation Village, San Diego.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education,

Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland, OR 97227. (503) 280-3200.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

February 25-29—**Eleventh Annual Family Practice Review.** Portland, Monday-Friday. Marriott Hotel. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OBSTETRICS AND GYNECOLOGY

October 22-24—**Third Annual Pacific Northwest Review of Obstetrics and Gynecology.** Portland, Monday-Wednesday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

SURGERY

December 7-8—**Recent Advances in Surgery.** Portland, Friday-Saturday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OF INTEREST TO ALL PHYSICIANS

September 14-15—**Newer Concepts in Cardiology.** Ashland, Friday-Saturday. Ashland Hills Motel. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

November 16-17—**Sixth Annual Symposium on Critical Care Medicine.** Portland, Friday-Saturday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

January 25-27—**Seminars in Cardiology.** Portland, Friday-Sunday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 16-20—**American College of Physicians Review Course.** Portland, Monday-Friday. Jantzen Beach Thunderbird. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 25-27—**Symposium on Sports Medicine.** Eugene, Wednesday-Friday. Thunderbird Motor Inn. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

August 8-10—**Sports Medicine.** Seattle. Wednesday-Thursday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

August 16-18—**Controversies in Otolaryngology.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

September 17-21—**Advances in Family Practice.** Seattle. Monday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

September 20-23—**Radiology Northwest III.** Seattle. Thursday-Sunday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

September 23-24—**Medical Problems in the Surgical Patient.** Walla Walla. Sunday-Tuesday. Walla Walla General Hospital. Contact: Sharon Werner, Walla Walla General Hospital, 933 Bonsella, Walla Walla, WA 99362. (509) 522-0480, Ext. 543.

September 27-29—**Plastic Surgery Repair for Primary MDs.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

October 5-6—**Scientific Program, Annual Meeting, Washington State Medical Association.** Seattle. Friday-Saturday. Washington Plaza Hotel. Contact: Mr. George Morford, Washington State Medical Association, 2033 Sixth Avenue, Seattle, WA. (206) 623-4801.

November 15-16—**Critically Ill Surgical Patient.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 28-29—**Northwest Stroke Symposium.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: Education and Training Department, Northwest Hospital, 1551 North 120th, Seattle, WA 98133. (206) 364-0500, ext. 686.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: 1980—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 23-27, 1980, Registry Resort, Scottsdale.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: February 7-13, 1980, Town and Country, San Diego.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 19-23, 1979, the Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 8-12, 1979, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual meeting: 1980—date and place to be announced.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 4-6, 1979, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 16-18, 1980, MGM Grand, Las Vegas.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: 1980—date and place to be announced.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Meeting: November 2-4, 1979, OMA Headquarters.

Utah State Medical Association—42 S. 5th East St., Salt Lake City 84102. Annual Meeting: September 11-14, 1979, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 4-7, 1979, Washington Plaza Hotel, Seattle.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: August 28-31, 1979, Jackson Lake Lodge, Moran.

ALASKA, MONTANA AND IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

July 25—**Herpes Genitalis—Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

August 22—**Dysplasia and Early Cervical Neoplasia**—Univ. of Wash. OB-GYN Sessions (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

MONTANA

August 3-4—**Montana Academy of Oto-Ophthalmology.** Kalispell. Friday-Saturday. Contact: Steve Weber, MD, P.O. Box 1080, Kalispell, MT 59901.

August 9-11—**Montana/Wyoming Chapter, American College of Surgeons' Annual Meeting**—Big Sky. Thursday-Saturday. Meadow Village. Contact: Charles F. Rinker, MD, 300 N. Willson, Bozeman, MT 59715. (406) 587-0704.

September 7-8—**Montana/Wyoming Chapter, American College of Physicians' Regional Meeting**—Fairmont Hot Springs, Friday-Saturday. Contact: J. E. McGreevey, MD, 401 S. Alabama, Butte, MT 59701. (406) 723-4384.

October 5-6—**American Cancer Society (Montana Chapter) Annual Meeting.** Billings. Friday-Saturday. Northern Hotel. Contact: Ruth Eaton, 2820 1st Ave. S., Billings, MT 59101.

October 11-13—**Montana Medical Association Annual Meeting.** Kalispell. Thursday-Saturday. Outlaw Inn. Contact: Montana Medical Association, 2021 Eleventh Ave., Suite 12, Helena, MT 59601. (406) 443-4000.

Index to
The Western Journal of Medicine Advertising

BANK OF AMERICA
Business Services 25
BURROUGHS WELLCOME CO.
Neosporin 23
CALYPSO SAILING ASSOCIATION AND SAILING SCHOOL 14
CLASSIFIED 24, 26
DATAMEDIC OF CALIFORNIA 3
DOCTOR'S COMPANY, THE 8
ELI LILLY AND COMPANY
V-Cillin K 27
ENDO LABORATORIES
Percocet-5 ..... 10, 11
FIRSTMARK CAPITAL CORPORATION 14
INTERNATIONAL MEDICAL EDUCATION
Medical Education Programs 12
MEAD JOHNSON PHARMACEUTICAL DIVISION
Colace 19
Vasodilan 20, 21
Quibron 22
MERCK SHARP & DOHME
Aldomet 10
MOUNT ZION HOSPITAL & MEDICAL CENTER
Symposium—Gynecologic & Breast Cancer: Current Concepts & Controversies 12
PHARMACEUTICAL MANUFACTURERS ASSOCIATION 6, 7
PHYSICIANS & SURGEONS INSURANCE EXCHANGE 15
ROCHE LABORATORIES
Librax ..... 2nd Cover, 1, 2
Valium ..... 3rd & 4th Covers
SANDOZ PHARMACEUTICALS
Hydergine 13
SMITH KLINE & FRENCH COMPANY
Tagamet 5
E. R. SQUIBB & SONS INC.
Pronestyl 17, 18
UNIVERSITY MICROFILMS INTERNATIONAL 28
UPJOHN COMPANY, THE
Motrin 9

WASHINGTON STATE EDITION
WSMA Reports (see 8-page tan section)

THE WESTERN Journal of Medicine

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VOLUME 131 • NUMBER 2 AUGUST 1979

85 *Extracardiac Manifestations of Bacterial Endocarditis* JOHN E. HEFFNER, MD

92 *Severe Neutropenia in Infectious Mononucleosis*
WILLIAM P. HAMMOND, MD; JOHN M. HARLAN, MD, and STEPHEN E. STEINBERG, MD

98 *Congenital Dislocation of the Hip—Prognostic Implications of Early Diagnosis*
SYLVAIN P. TERVER, MD; RONALD M. CONSTINE, MD; JOHN CSONGRADI, MD; RICHARD KLEINMAN, MD, and EUGENE E. BLECK, MD

MEDICAL PROGRESS
104 *Recent Advances in Antidepressant Drug Treatment* STEPHEN E. ERICKSEN, MD

SPECIALTY CONFERENCE
114 *The Relative Contributions of Nature and Nurture in Chronic Obstructive Pulmonary Disease*
Discussant: A. SONIA BUIST, MD
Medical Grand Rounds, Department of Medicine, University of Oregon Health Sciences Center

MEDICAL STAFF CONFERENCE
122 *Pulmonary Aspiration* Chief Discussant: JOHN W. LITTLE, MD

IMPORTANT ADVANCES IN CLINICAL MEDICINE
130 *Physical Medicine and Rehabilitation—Epitomes of Progress*

EDITORIALS
135 • *How Much Freedom Do We Really Have?* • *Routine Spirometric Testing and COPD* • *Tel-Med* • *More Effective Use of Antidepressants*

CASE REPORTS
140 *Hyperhistaminemia and Peptic Ulcer* JON D. HIRASUNA, MD; IRWIN SHELUB, MD, and ROBERT J. BOLT, MD

143 *Necrotic Arachnidism* BARBARA STOCHOSKY, MD

148 *Deliberate Abuse of Diphenoxylate Hydrochloride, a Schedule V Narcotic*
JONATHAN S. RUBINSTEIN, MD

150 *Epiglottitis in an Immunosuppressed Host*
JOHN H. COCHRAN, JR., MD; WILLARD E. FEE, JR., MD, and AUBREY MAZE, MD

152 *Leukoerythroblastic Reaction in Still Disease in an Adult*
GARY S. LAZAR, MD, and STEPHEN J. FORMAN, MD

CORRESPONDENCE
156 • *The Safety of Agricultural Chemicals* • *The Plight of Tithonus* • *Functional Overlay* • *Removal of Retained Gallstones; With Reply by Author* • *Evidence in Medicine as a Natural Science* • *A Technique to Prevent Headaches After Diagnostic Lumbar Puncture*

IN THE FOREFRONT
162 *Tel-Med—A Success Story* W. BENSON HARER, JR., MD

INFORMATION
165 *Mania in Criminal Populations* THOMAS R. STAPLETON, MD

166 *Pain Clinic Model for Community Practice*
FRAN PEPITONE-ROCKWELL, PhD; RICHARD ROSENBLATT, MD, and GUY CORKILL, MD

171 *Articles To Read in Other Journals*

172 *Book Reviews*

177 *In Memoriam*

★ CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII; OREGON; WASHINGTON; ALASKA, MONTANA AND IDAHO
(See Advertising Page 32)

★★ Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association and the Washington State Medical Association

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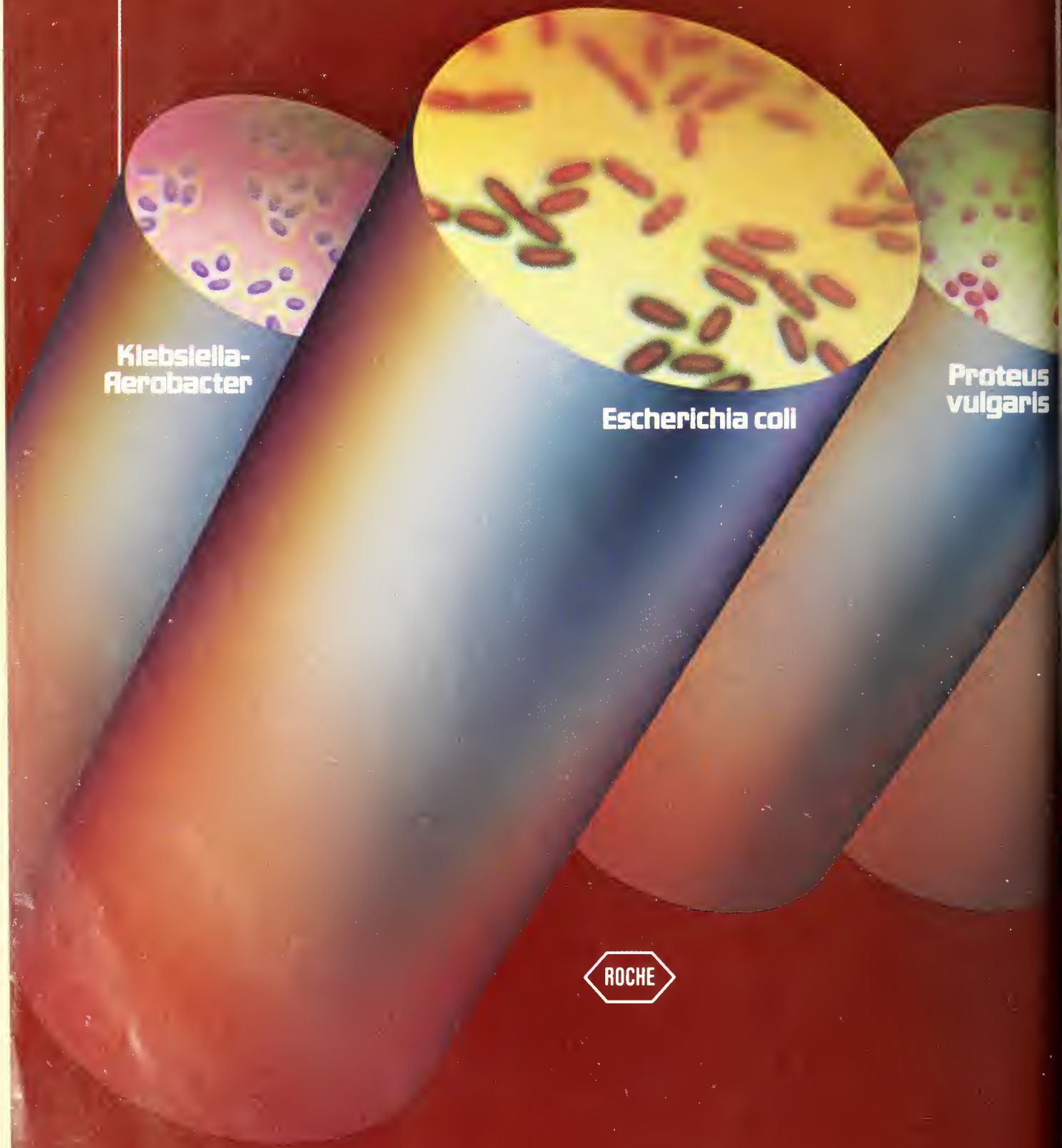

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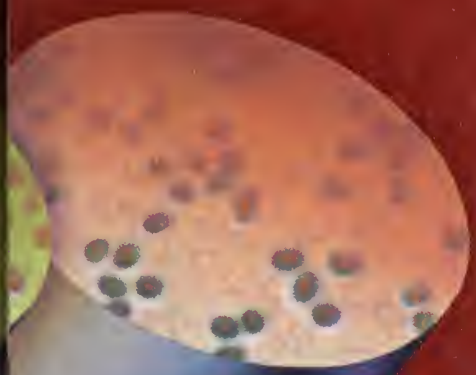

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Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis). *Usual adult dosage:* 2 Gm (2 DS tabs or 4 tabs or 4 teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.
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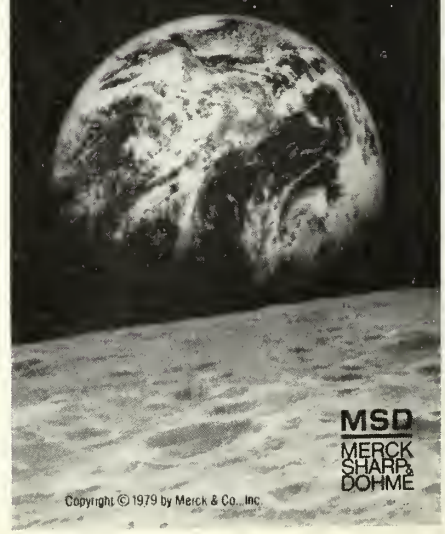

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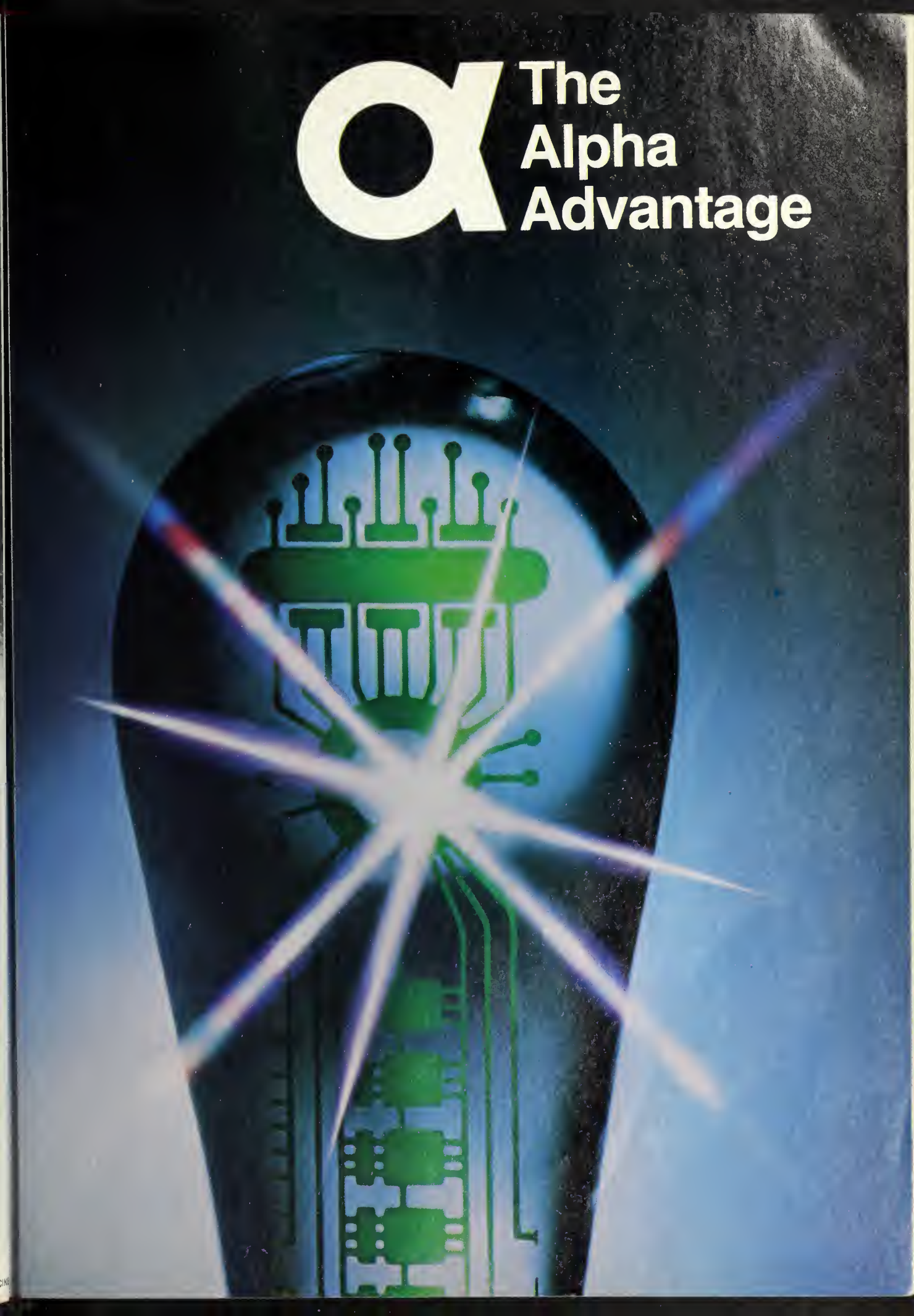


Alpha Stimulation

Central Control of Blood Pressure*

*The Family of Man by Roberto Moretti
a statuary in crystal symbolizing the broad range of
hypertensive patients eligible for therapy with Catapres.

The Alpha Advantage:

It's for all kinds of hypertensives

- *Unlike beta blockers, Catapres® has no contraindications.*
- *Catapres can be useful even in these patients with:*

Congestive heart failure	Allergic rhinitis
Ventricular hypertrophy	Hepatic disease
Hyperglycemia	Hyperuricemia
Diabetes mellitus	Gouty arthritis
Bronchial asthma	Sulfonamide hypersensitivity

Like any antihypertensive, use with caution in severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

work/play—normal hemodynamic responses to exercise maintained.

love—low incidence of impotence and/or loss of libido: 2.8% in 1,923 patients studied.[1]

cardiac output—tends to return to control values during long-term therapy.

blood flow—preserved in kidney.

No Single Advantage Determines Drug Choice.

Other factors must include:

The drug's effectiveness in a given patient, its side effects, warnings, precautions, tolerance, etc. A rational therapeutic choice depends on a careful assessment of all such factors.

*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

1. Data on file at Boehringer Ingelheim Ltd.

Please see last page for brief summary, including warnings, precautions, and adverse reactions.

Tablets of 0.1 mg and 0.2 mg

Catapres®

(clonidine HCl)

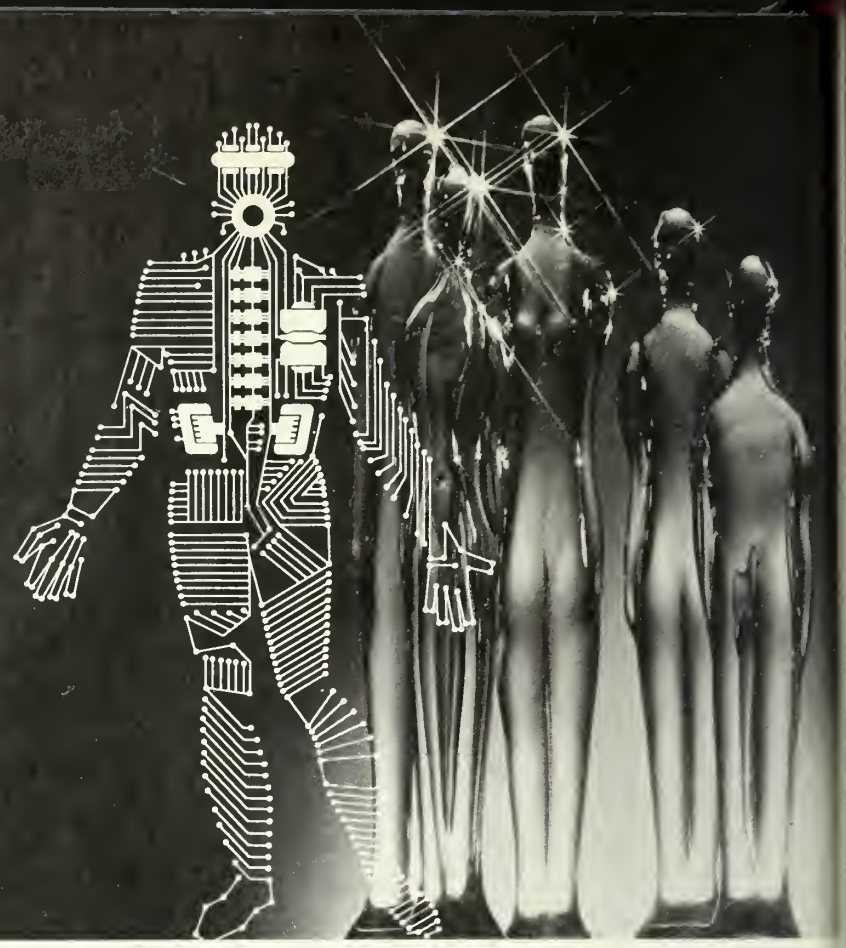
HYPERTENSION

The Alpha Advantage:

It's for all kinds of hypertensives

Tablets of 0.1 mg and 0.2 mg

Catapres®
(clonidine HCl)
HYPERTENSION



- No contraindications.
- Effective in all degrees of hypertension. It is mild to moderate in potency.
- Low incidence of depression, impotence, orthostatic hypotension—no fatal hepatotoxicity.
- Preserves kidney blood flow.

Most common side effects are dry mouth, drowsiness, and sedation which generally tend to diminish with time.

The usual starting dose of Catapres is 0.1 mg at breakfast and 0.1 mg at bedtime. Some patients may benefit from a starting dose of 0.1 mg at bedtime.

Usual daily dose range—0.2—0.8 mg

Maximum daily dose—2.4 mg (12 tablets of 0.2 mg). Doses as high as this have rarely been employed.

For optimal results, the dose of Catapres must be adjusted according to the patient's individual blood pressure response.

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase: congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes: nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres, (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.
For complete details, please see full prescribing information.
Under license from Boehringer Ingelheim GmbH

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Boehringer Ingelheim

Boehringer Ingelheim Ltd
Ridgefield, CT 06877

Personally, Steve could never speak up for milk.

In TV commercials, you'll often see people speaking up for milk. Steve Allen and his wife Jayne Meadows are also seen on TV telling viewers about Mocha Mix... 100% milk free!

Matter of fact, this non-dairy creamer would have been found in their home way before they ever filmed the Mocha Mix series of commercials. Steve is allergic to milk products. Yet, he likes the splash of luxury and fresh taste in his coffee, on cereal, fruit and dessert, even in cooking. For the Allen household, Mocha Mix is the perfect answer.

It could well be the answer for many people who rely on you for their dietary needs, those with an allergy similar to Steve's, or a lactose intolerance. And, for many who must maintain a fat-restricted diet you should know that Mocha Mix is one non-dairy creamer that contains no coconut oil, giving it the highest ratio of unsaturated to saturated fat of any creamer. It easily exceeds the accepted standard 2:1 ratio. It's 100% cholesterol free, too. No wonder Mocha Mix is not just another non-dairy creamer, but the one you can rely on most for your patients who can't speak for milk, either.

NUTRITION INFORMATION

Portion Size 1 Fluid Ounce (2 Tbs.)
Servings Per Container 16
Calories 40
Protein . . . . . 0 grams
Carbohydrate . . . . . 3 grams
Fat . . . . . 3 grams
Percent of Calories from Fat 73%
Polyunsaturated Fat . . 1 gram
Saturated Fat . . . . . 0 grams
Cholesterol (Δ) . . . . . 0 mg (0 mg/100g)

In addition to the pint and quart size found in the dairy case of most grocery stores, Mocha Mix is available in 4 ounce and ½ oz. portion packs for hospitals and institutions.

Interested? Send us a note and we will send you a supply of coupons your patients can redeem at their grocers. Hospital service may also be supplied upon request. Mail to: Mocha Mix Dept. Presto Food Products, Inc. P.O. Box No. 21908, Los Angeles, Calif. 90021

Percentage of U.S. Recommended Daily Allowance (U.S. RDA)*

*Contains less than 2% of the U.S. RDA of Protein, Vitamin A, Vitamin C, Thiamine, Riboflavin, Niacin, Calcium, Iron.

ΔInformation on fat and cholesterol content is provided for individuals who, on the advice of a physician, are modifying their total dietary intake of fat and cholesterol.

mocha mix®

. . . the non-dairy creamer that's lowest in saturated fat.

an important in the treatment of

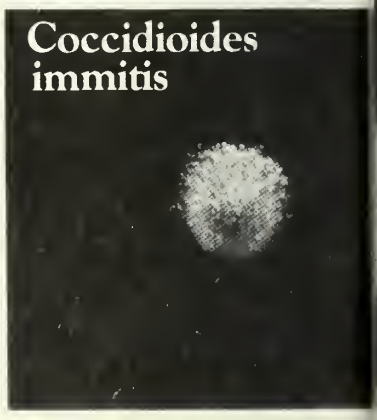
Efficacy of MONISTAT i.v. therapy...

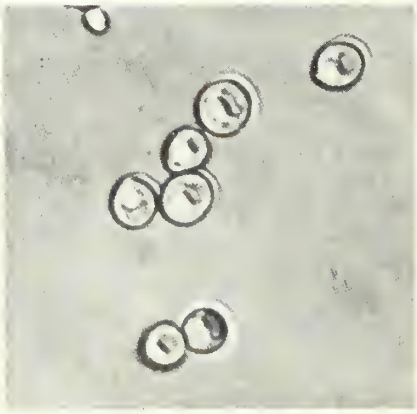
highly favorable rates of recovery or clinical improvement

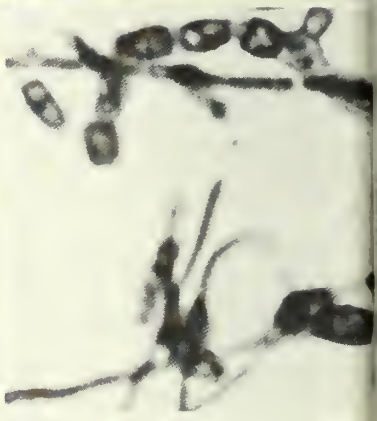
- effective against systemic candidiasis
  chronic mucocutaneous candidiasis
  coccidioidomycosis
  cryptococcosis
  paracoccidioidomycosis
- in patients who did not respond to amphotericin B therapy
- in immunologically-compromised patients with severe infections

rapid onset of clinical improvement
In most patients who responded, improvement was observed within 1-3 weeks of MONISTAT i.v. therapy; however, prolonged treatment courses may be necessary to prevent relapse.

no development of fungal resistance during therapy reported
In vitro resistance of clinical isolates has not been observed during clinical trials.







Photos courtesy of Dubos, J. R., Bacterial and Mycotic Infections of Man, J. B. Lippincott Company, 1968 and Burrows, W., Textbook of Microbiology, W. B. Saunders Company, 19th edition.

and the side effect profile

no nephrotoxicity or other permanent adverse effects in clinical studies

- even in prolonged therapy
- even in patients with renal disease

extensively evaluated
During clinical trials in over 400 patients, no permanent adverse reactions were reported.

Adverse reactions
MONISTAT i.v. should not be administered undiluted. Rapid injection of the undiluted solution may produce transient tachycardia or arrhythmia.
Adverse reactions include phlebitis, pruritus, rash, nausea, vomiting, febrile reactions, drowsiness, diarrhea, anorexia and flushes. Transient hematologic changes have occurred; therefore, the patient should be closely monitored.

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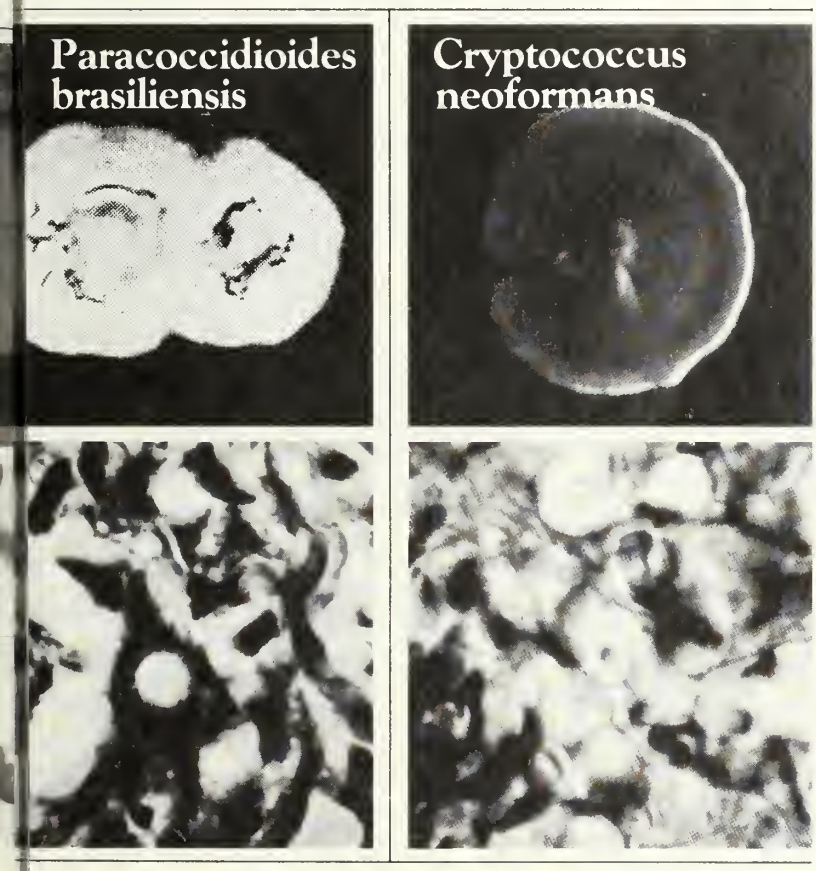
advancement systemic mycoses



generally well tolerated by severely debilitated patients

- cancer patients
- patients receiving immunosuppressive drugs
- patients with serious underlying conditions such as renal insufficiency or diabetes mellitus

for more information

Because of the uniqueness of MONISTAT i.v. only some of the highlights can be presented in this advertisement. For more information, i.e., product monograph, dosage schedules, etc., please fill out the coupon on the next page and mail to Ortho Pharmaceutical Corporation.

Please turn page for Prescribing Information

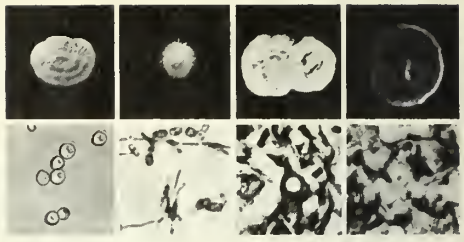
Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

Monistat i.v.
TRADEMARK

(miconazole)

broad-spectrum activity against major systemic fungal pathogens

in systemic fungal infections...



Monistat i.v.
TRADEMARK

(miconazole)

a broad-spectrum systemic antifungal agent

DESCRIPTION: MONISTAT i.v. (miconazole) 1-{2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl) methoxyl ethyl} 1 H-imidazole is a synthetic antifungal supplied as a sterile solution for intravenous infusion. Each ml of this solution contains 10 mg of miconazole with 0.115 ml PEG 40 castor oil, 1.0 mg lactic acid USP, 0.5 mg methylparaben USP, 0.05 mg propylparaben USP in water for injection. Miconazole i.v. is a clear, colorless to slightly yellow solution having a pH of 3.7 to 5.7.

CLINICAL PHARMACOLOGY: MONISTAT i.v. is rapidly metabolized in the liver and about 14% to 22% of the administered dose is excreted in the urine, mainly as inactive metabolites. The pharmacokinetic profile fits a three-compartment open model with the following biologic half-life: 0.4, 2.1, and 24.1 hours for each phase respectively. The pharmacokinetic profile of MONISTAT i.v. is unaltered in patients with renal insufficiency, including those patients on hemodialysis. The in/vitro antifungal activity of MONISTAT i.v. is very broad. Clinical efficacy has been demonstrated in patients with the following species of fungi: *Coccidioides immitis, Candida albicans, Cryptococcus neoformans, and Paracoccidioides brasiliensis.*

Recommended doses of MONISTAT i.v. produce serum concentrations of drug which exceed the in-vitro MIC values for the fungal species noted above. Doses above 9 mg/kg of MONISTAT i.v. produce peak blood levels above 1 μg/ml in most cases. The drug penetrates into joints.

INDICATIONS: MONISTAT i.v. is indicated for the treatment of the following severe systemic fungal infections: coccidioidomycosis, candidiasis, cryptococcosis, paracoccidioidomycosis, and for the treatment of chronic mucocutaneous candidiasis. However, in the treatment of fungal meningitis and urinary bladder infections an intravenous infusion alone is inadequate. It must be supplemented with intrathecal administration and bladder irrigation. Appropriate diagnostic procedures should be followed and MICs should be determined.

MONISTAT i.v. should not be used to treat common trivial forms of fungal diseases.

CONTRAINDICATIONS: MONISTAT i.v. is contraindicated in those patients who have shown hypersensitivity to it.

WARNINGS: Rapid injection of undiluted MONISTAT i.v., may produce transient tachycardia or arrhythmia.

PRECAUTIONS: Before a treatment course of MONISTAT i.v. is started, the physician should make sure that the patient is not hypersensitive to the drug product. MONISTAT i.v. should be given by intravenous infusion. The treatment should be started under stringent conditions of hospitalization but subsequently may be given to suitable patients under ambulatory conditions with close clinical monitoring. It is recommended that an initial dose of 200 mg be given with the physician in attendance. It is also recommended that clinical laboratory monitoring including hemoglobin, hematocrit, electrolytes and lipids be performed.

It should be borne in mind that systemic fungal mycoses may be complications of chronic underlying conditions which in themselves may require appropriate measures.

Pregnancy: Reproductive studies with MONISTAT i.v. in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus. There are no data, however, on the use of the drug in pregnant women.

Children: Since the safety of miconazole i.v. in children under one year of age has not been extensively studied, its benefits in this age group must be weighed against the possible risks involved.

ADVERSE REACTIONS: Adverse reactions which have been observed with MONISTAT i.v. therapy include phlebitis, pruritus, rash, nausea, vomiting, febrile reactions, drowsiness, diarrhea, anorexia and flushes. In the U.S. studies, 29% of 209 patients studied had phlebitis, 21% pruritus, 18% nausea, 10% fever and chills, 9% rash, and 7% emesis. Transient decreases in hematocrit and serum sodium values have been observed following infusion of MONISTAT i.v. Thrombocytopenia has also been reported. No serious renal or hepatic toxicity has been reported. If pruritus and skin rashes are severe, discontinuation of treatment may be necessary. Nausea and vomiting can be mitigated with antihistaminic or antiemetic drugs given prior to MONISTAT i.v. infusion, or by reducing the dose, slowing the rate of infusion, or avoiding administration at mealtime.

Aggregation of erythrocytes or rouleau formation on blood smears has been reported. Hyperlipemia has occurred in patients and is reported to be due to the vehicle. Cremophor EL (PEG 40 castor oil).

DRUG INTERACTIONS: Drugs containing cremophor-type vehicles are known to cause electrophoretic abnormalities of the lipoprotein. These effects are reversible upon discontinuation of treatment but are usually not an indication that treatment should be discontinued.

Interaction with the coumarin drugs resulting in an enhancement of the anticoagulant effect has also been reported. In cases of simultaneous treatment with MONISTAT i.v. and coumarin drugs, the anticoagulant effect should be carefully titrated since reductions of the anticoagulant doses may be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE

Adults. The doses may vary with the diagnosis and with the infective agent, from 200 to 1200 mg per infusion. The following daily doses, which may be divided over 3 infusions, are recommended:

Organism	Dosage Range*	Duration of Successful Therapy (weeks)
Coccidioidomycosis:	1800 to 3600 mg per day	3 to > 20
Cryptococcosis:	1200 to 2400 mg per day	3 to > 12
Candidiasis:	600 to 1800 mg per day	1 to > 20
Paracoccidioidomycosis:	200 to 1200 mg per day	2 to > 16

* May be divided over 3 infusions.

Repeated courses may be necessitated by relapse or reinfection.

Children: A total daily dose of about 20 to 40 mg/kg is generally adequate. However, a dose of 15 mg/kg body weight per infusion should not be exceeded.

ADMINISTRATION: MONISTAT i.v. should be diluted in at least 200 ml of fluid. The diluent of choice is 0.9% sodium chloride or alternatively Dextrose 5% injectable solution. The intravenous infusion should be given over a period of 30 to 60 minutes.

Generally, treatment should be continued until all clinical and laboratory tests no longer indicate that active fungal infection is present. Inadequate periods of treatment may yield poor response and lead to early recurrence of clinical symptoms. The dosing intervals and sites and the duration of treatment vary from patient to patient and depend on the causative organism.

OTHER MODES OF ADMINISTRATION: Intrathecal. Administration of the undiluted injectable solution of MONISTAT i.v. by the various intrathecal routes (20 mg per dose) is indicated as an adjunct to intravenous treatment in fungal meningitis. Succeeding intrathecal injections may be alternated between lumbar, cervical, and cisternal punctures every 3 to 7 days. Bladder instillation of 200 mg of diluted solution is indicated in the treatment of mycoses of the urinary bladder.

HOW SUPPLIED: MONISTAT i.v. is supplied in 20 ml ampoules.

MONISTAT i.v. (miconazole) is an original product of Janssen Pharmaceutica N.V., Belgium, and co-developed by Ortho Pharmaceutical Corporation.

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

WJ8/79

Ortho Pharmaceutical Corporation
c/o 733 Summer Street
Stamford, CT 06901

Please send me more information on the broad-spectrum, systemic antifungal agent... MONISTAT i.v. (miconazole).

_____ M.D.

Address _____

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Specialty _____

October 1978

The primary beneficiaries of ORAL HYDERGINE® TABLETS, 1 mg (1 tab t.i.d.)

Each 1 mg Hydergine tablet contains dihydroergocornine mesylate 0.333 mg, dihydroergocristine mesylate 0.333 mg, and dihydroergocryptine (dihydro-alpha-ergocryptine and dihydro-beta-ergocryptine in the proportion of 2:1) mesylate 0.333 mg, representing a total of 1 mg.

They're in their late sixties, the beneficiaries of more liberal retirement laws and more enlightened attitudes toward the elderly. They're leading socially productive lives. But recently, without any clear cause, they had each begun to experience mild episodes of symptoms such as confusion, mood-depression, and dizziness. Their ability to function could have been jeopardized. That's when they became the beneficiaries of oral Hydergine therapy.

The still-functioning geriatric can benefit from Hydergine treatment

It is quite common for cognitive and emotional symptoms of deterioration to manifest gradually in the elderly. During this early stage, such symptoms are mild and more amenable to treatment. It is at this stage that Hydergine therapy has proved most effective. Patients tend to respond better, and with symptoms effectively relieved—or at least their progression retarded—the ability to function can be maintained.

Oral Hydergine tablets promote better patient compliance

Compared with the sublingual form, dosage administration is easier, with less need for supervision.

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Contraindications: Hypersensitivity to the drug.
Precautions: *Because the target symptoms are of unknown etiology, careful diagnosis should be attempted before prescribing Hydergine tablets and sublingual tablets.*
Adverse Reactions: Serious side effects have not been found. Some sublingual irritation, transient nausea, and gastric disturbances have been reported. Hydergine tablets and sublingual tablets do not possess the vasoconstrictor properties of natural ergot alkaloids.
Dosage and Administration: 1 mg three times daily. Alleviation of symptoms is usually gradual and results may not be observed for 3–4 weeks.
How Supplied: Hydergine tablets (for oral use) 1 mg, packages of 100 and 500. **Hydergine sublingual tablets 1 mg,** containing dihydroergocornine mesylate 0.333 mg, dihydroergocristine mesylate 0.333 mg, and dihydroergocryptine (dihydro-alpha-ergocryptine and dihydro-beta-ergocryptine in the proportion of 2:1) mesylate 0.333 mg, representing a total of 1 mg; packages of 100, 500, and 1000. **Hydergine sublingual tablets 0.5 mg,** containing dihydroergocornine mesylate 0.167 mg, dihydroergocristine mesylate 0.167 mg, and dihydroergocryptine (dihydro-alpha-ergocryptine and dihydro-beta-ergocryptine in the proportion of 2:1) mesylate 0.167 mg, representing a total of 0.5 mg; packages of 100 and 1000.
Before prescribing, see package insert for full product information.

SANDOZ PHARMACEUTICALS, EAST HANOVER, N.J. 07936

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The Great Laxative Escape

This asthmatic isn't worried about his next breath...

he's active he's effectively maintained on

QUIBRON®

Each capsule or tablespoonful (15 ml) liquid contains theophylline (anhydrous) 150 mg and glyceryl guaiacolate (guaifenesin) 90 mg

- theophylline for effective around-the-clock bronchodilator therapy
- 100% free theophylline

Indications: For the symptomatic relief of bronchospastic conditions such as bronchial asthma, chronic bronchitis, and pulmonary emphysema

Warnings: Do not administer more frequently than every 6 hours, or within 12 hours after rectal dose of any preparation containing theophylline or aminophylline. Do not give other compounds containing xanthine derivatives concurrently.

Precautions: Use with caution in patients with cardiac disease, hepatic or renal impairment. Concurrent administration with certain antibiotics, i.e., clindamycin, erythromycin, troleandomycin, may result in higher serum levels of theophylline. Plasma prothrombin and factor V may increase, but any clinical effect is likely to be small. Metabolites of guaifenesin may contribute to increased urinary 5-hydroxyindoleacetic acid readings, when determined with nitrosonaphthol reagent. Safe use in pregnancy has not been established. Use in case of pregnancy only when clearly needed.

Adverse Reactions: Theophylline may exert some stimulating effect on the central nervous system. Its administration may cause local irritation of the gastric mucosa, with possible gastric discomfort, nausea, and vomiting. The frequency of adverse reactions is related to the serum theophylline level and is not usually a problem at serum theophylline levels below 20 mcg/ml

How Supplied: Capsules in bottles of 100 and 1000 and unit-dose packs of 100; Liquid in bottles of 1 pint and 1 gallon.

See package insert for complete prescribing information.

Mead Johnson PHARMACEUTICAL DIVISION

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WSMA REPORTS

Washington State Medical Association

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(206) 623-4801
1-800-552-0612

August 1979

Contents

2 Statewide Medical Marijuana Program Scheduled to Start in September

3 Amendment Proposed to WSMA Constitution

4 Migrant Children Receive Aid Through Migrant Health Project

5 "Fun Run" for Physicians Part of Sports Calendar at Annual Meeting

6 Rubella Prevention a Must for Women of Child Bearing Age

7 Scientific Sessions at WSMA Annual Meeting Listed

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Guest Editorial

Technology Assessment: A Tool for Quality Patient Management?

Medicine is both Art and Science. The Art is intuitive, compassionate and mystical. The Science is certain, objective and quantifiable. The disparity between the Art and the Science of Medicine is fundamental to the "National Crisis in Medical Care"—the yearning for Old Doc, but insistence on the new shiny-bright technology. The crisis is a crisis of choices, once only prayed for, now blessedly available.

Everybody—patients and public, government, labor and business alike—complains about the escalating costs of medical care, blithely or schizophrenically ignoring the fact that much of that exponentially increasing cost in the new technology is applied to our increasingly elderly population where each victory carries with it the burden of a later, more costly battle. The cheap technologic victories were with infections in the young—strep throat, pneumonia, polio. The battles now and in the future are with degenerative diseases of the elderly—cancer and cardiovascular disease, and the threat to the public purse is alarming.

The good physician, committed to the needs of his patients, applies technology at whatever cost, if it will help his patient, not utilizing it only if the complex of social and ethical factors in his patients does not require it. The Hippocratic allegiance to the patient supersedes that to the public and to the country.

In fascination with ever-newer technology, third-party payers have eagerly paid more for the Science and less for the Art, for the procedure, but not for the time and opinion required in the management of technology.

Meanwhile, Government and Industry have other designs on the ten percent of GNP generated by health care. Part of the strategy to chop and relocate that ten percent is rationing through HSA's, HMO's and the National Center for Health Care Technology, all of which have laudable qualities. The HSA, HMO and technology assessment have a common virtue to the budget (and to the politician) of creating a scapegoat to ration the new technology.

(cont'd on p. 8)

Medical Marijuana Program to Start in Fall

Use of marijuana for certain medical purposes was approved by the 1979 Washington State Legislature with the passage of House Bill 259. The bill allows cancer patients suffering from nausea and other ill effects of chemotherapy to receive marijuana under a controlled substances therapeutic research program. While glaucoma patients and cancer patients receiving only radiation therapy may also be included, at this time research will be limited to those undergoing chemotherapy.

HB 259 calls for a research program because marijuana is classified as a Schedule I substance by the federal Food and Drug Administration, and therefore can be used only for approved research purposes. Since legislators passed HB 259, a state research protocol has been written; Drs. Fred Appelbaum and Philip Greenberg, assistant professors in the University of Washington Division of Oncology, wrote much of the medical section of the protocol. Dr. David L. Dunner, chief of psychiatry at Harborview Medical Center and professor in the UW Department of Psychiatry and Behavioral Sciences, also helped write the protocol and agreed to be principal investigator for the program.

Dr. Dunner says the protocol has been reviewed and approved by the UW Human Subjects Review Committee, and he expects final approval by the FDA soon. As a result, the state program will receive pure supplies of the drug from the National Institute on Drug Abuse.

The principal active ingredient in marijuana is delta-9-tetrahydrocannabinol (THC). The research program is designed to determine the antiemetic properties of delta-9-THC when used with a placebo or with Compazine (prochlorperazine), a commonly used antiemetic drug. Patients will voluntarily agree to take the delta-9-THC, but they will not know whether they are taking it with a placebo or with Compazine.

Delta-9-THC will be administered in capsules to most patients, although cigarettes will also be available. Patients with a known sensitivity to Compazine will be able to receive Delta-9-THC alone.

Any physician in the state who is caring for cancer patients undergoing chemotherapy is eligible to participate in the program. The program is expected to begin in September.

Dr. Dunner said that physicians wishing their patients to be included in the program should call him (206-223-3404) or write to him (ZA-31, Harborview Medical Center, 325 Ninth Avenue, Seattle 98104). Forms will be sent to the physician which will include questions to be answered by the physician on the patient's past and present medical condition. The patient will fill out a personal medical history and answer questions regarding his psychiatric status. The patient will also be required to sign an informed consent form before he enters the program.

Once the forms have been returned, they will be reviewed by the patient qualification review committee composed of an ophthalmologist, oncologist, psychiatrist and radiologist. Dr. Dunner will be the psychiatrist member of the committee. "We have tried to devise the program so there is a minimum of paperwork for both physician and patient," he said. "We expect to process the forms quickly and have an answer to the physician within a week of receipt of completed forms. If there are no contraindications, the patient will be included in the program, and I will notify the state board of pharmacy to ship the drug to the physician."

Contraindications include pregnancy, cardiovascular disease and high bilirubin. Patients with a history of schizophrenia may also be excluded. Children under the age of five are excluded, and minors below the age of 18 must have parental approval.

Although there is a minimum of paperwork involved in participating in the program, Dr. Dunner said a condition of continuing in the study will be to keep proper medical records. Both physician and patient

Dr. David L. Dunner

will be required to answer questions on the effects of the drug; the patient will be asked to keep a record of his own clinical response including the drug's effects on nausea and appetite and the "high" effect.

Since many cancer patients are middle-aged or older and probably have not tried marijuana before, Dr. Dunner recommends that the first trial of delta-9-THC be taken in the physician's office under his or her supervision. He noted that some studies have shown that patients get "high" or become confused when given an amount sufficient to have an antiemetic effect.

After an initial trial under physician supervision, patients may take the drug at home. They should be advised, Dr. Dunner said, to take the drug in the company of a family

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member or friend and they should not drive until 24 hours following the last dose of delta-9-THC.

Patients are to take the drug at the beginning of a course of chemotherapy and continue it at specified intervals throughout the course. Dosages, determined from other research studies, will be based on body surface. If there is no effect, the dosage may be increased, and if there is a deleterious effect, the dosage will be decreased.

One group of approximately 40 patient-volunteers hospitalized in one location will be studied to determine changes in blood level of the drug compared to clinical response.

Dr. Dunner anticipates that about 500 patients will be needed to statistically answer the program's research question on delta-9-THC's antiemetic effectiveness. He said, "We need that relatively large number because of the number of variables present: different kinds of cancers, different kinds of chemotherapies and different ages.

"The success of the program will depend very directly on the number of physicians and patients willing to participate."

Prime sponsor of HB 259 was Rep. Ted Haley of Tacoma, a physician. He said he introduced the bill "for humanitarian reasons and because of popular demand." He explained, "I heard from many cancer patients who told me of marijuana's antiemetic effects and who were distressed at having to obtain it illegally." Testimony by cancer chemotherapists and others convinced legislators that marijuana is a useful drug, he added.

Roger Roffman, University of Washington associate professor in the School of Social Work, was among those who testified for the bill. Roffman teaches UW graduate courses in alcohol and drug abuse and has been studying marijuana use for more than a decade. He said he lobbied for the bill "because I have seen so much suffering connected with chemotherapy that could be allieviated by this drug. I talked with many people who were undergoing chemotherapy who had used marijuana, and I began to realize it was indeed effective in combating nausea. I expect a lot of patients to be helped by legalized medical use of the drug. It definitely works, although not for everybody. But no drug helps everybody." He has been named special advisor to the board of pharmacy for implementation of the new law.

Roffman recently wrote a pamphlet for patients entitled "Using Marijuana in the Reduction of Nausea Associated with Chemotherapy" that contains a detailed explanation of what patients can expect in using the drug. (The pamphlet can be ordered from Murray Publishing Company, 2312 Third Avenue, Seattle 98121.) He is now producing a flyer to brief physicians on the project; it and patient application forms will be available by early September.

He noted that the major known side effect of using delta-9-THC is intoxication. He said that the possibility of having a dysphoric experience ("bad trip") seems to depend on the "psychological atmosphere surrounding the patient. Patients who are fearful or ignorant about the drug have an increased likelihood of having a dysphoric experience; those who are well-informed about the drug and are relaxed are more likely to have a good experience."

Roger Roffman

Roffman said he hopes "the medical profession will recognize the unique nature of the drug and its usefulness to patients." He noted that 15 states will soon have medical marijuana programs, most of them involving research protocols. "Further research is needed," he acknowledged, "but marijuana's use as a folk medicine goes back more than 5,000 years."

At the end of 24 months, a report on the program will be submitted to the state legislature for its evaluation. Dr. Dunner said the report by this state program, along with other research reports, should answer questions about delta-9-THC's efficacy and could lead ultimately to the FDA changing its classification to a prescription drug.

Proposed Amendment to WSMA Constitution

The 1978 WSMA House of Delegates referred the following amendment to the WSMA Constitution to the House for final action in 1979. (First of two official publications):

Article VIII, Section 5—Judicial Council. The Judicial Council shall be the final ((appeal within WSMA)) *appellate body within this Association* in interpreting the WSMA Constitution and Bylaws. ((grievances, disciplinary, or remedial action, mediation and ethical opinions. The Judicial Council will provide a contemporary screening of ethics and guidelines.))

Portions of the section presented for amendment enclosed within (( )) are parts to be deleted from the Constitution, and those parts italicized are the portions to be added by the proposed amendment.

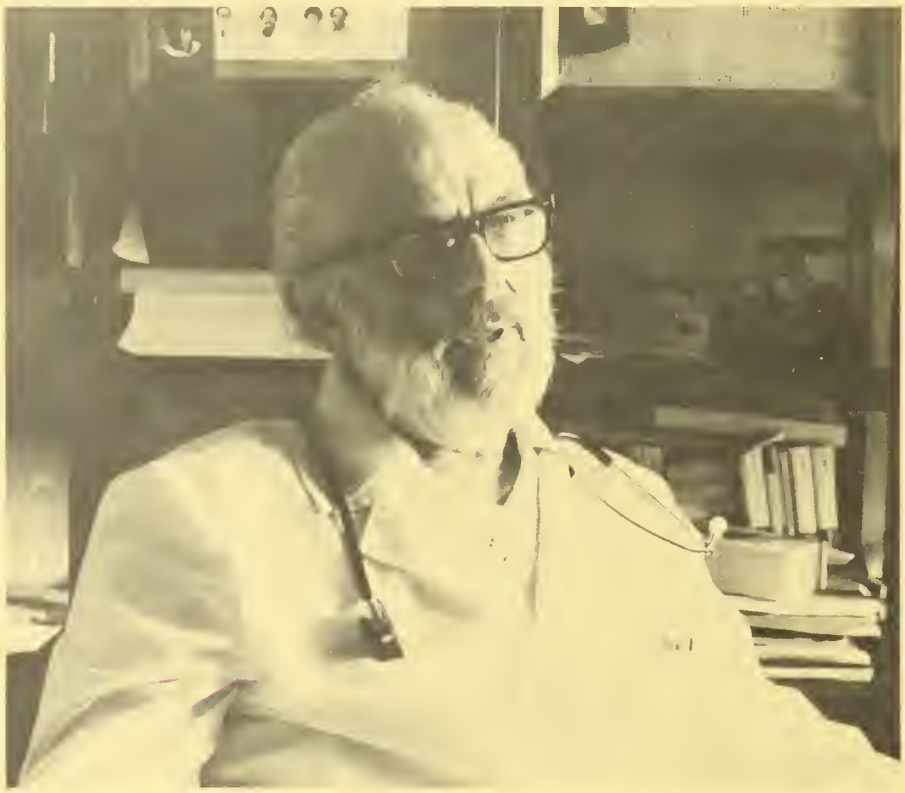
Migrant Children Helped by Health Project

Anemia, upper respiratory infections, otitis media with associated hearing loss, dental caries and skin and eye disease are almost endemic among children of migrant farm workers. While the federal Title I Migrant Education Program, started in 1966, calls for health screening of these children, until very recently little has been done in a systematic way to improve their health status.

Efforts to date have been fragmented for a variety of reasons, says Dr. Robert Tidwell, Seattle pediatrician. School nurses who see many migrant children generally do not have the time to do adequate screenings simply because of the numbers of children involved. Federally funded rural health clinics are supposed to serve all farm workers, not solely migrants, and they may be inaccessible to migrants anyway. Migrant children generally do not fall into the state Medicaid program, Dr. Tidwell said, and it is reported that some physicians simply do not want migrants in their offices. Finally, language barriers frequently have been effective in shutting migrants out of the health care system, he said.

With those factors in mind, Dr. Tidwell devised a state migrant health pilot program last summer to develop data on the health status of migrant children and to devise a coordinated approach to screening, examination and followup. The project was designed to build on existing local agency health services and to seek the cooperation of local health care professionals.

A mobile van, equipped much like a physician's office and staffed by a bilingual registered nurse, an LPN and an outreach worker/van driver circulated among the Yakima Valley communities of Mabton, Sunnyside, Harrah, Wapato, Grandview and Toppenish over a six-week period. Dr. Tidwell and Dr. Gary Spector joined the van for approximately two days each week.



Dr. Robert Tidwell, medical director of migrant health program.

With the cooperation of health care workers in those communities, examinations were conducted wherever there were concentrations of children—in public schools offering summer school to migrant children, in day care centers, in churches and in the migrant camps.

Parents were notified when screenings would be done in their area and they signed consent forms—written in English and Spanish—for examination and treatment. During the project 825 migrant children, ranging from infants to age 17, received a complete physical evaluation. Of those 629 received a physical evaluation by a physician, and 492 were immunized. All of the children were given TB tests. More than half of the children had a demonstrable health problem; anemia was the most common.

"Parents' response to the program was excellent," Dr. Tidwell commented, "and many parents came back after the child's examination to discuss their children's health problems."

Detailed medical records were kept by project workers so that a data base could be developed. The records were also entered in the Migrant Student Record Transfer System (MSRTS), a national data bank which attempts to collect health and educational information on every migrant child.

In January, 1979, the pilot was expanded to a year round program funded by a Title I grant, and Dr. Tidwell was named medical director of the program. Using the pilot project as a model, the program is now traveling to migrants in the Yakima Valley, the Columbia Basin, Wenatchee, Mt. Vernon and Bainbridge Island. Approximately 3,000

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migrant children will be screened this year. A nurse practitioner has been added to the traveling staff, and she is able to treat patients and write prescriptions under Dr. Tidwell's supervision. The program also has contracted with physicians and rural health clinics to do examinations for $5 to $12 per examination. Dr. Tidwell now joins the van on an on-call basis.

Program staff have continued to uncover numerous health problems among the migrant children, he said. Earlier this summer 109 migrant teenagers living in Pasco were screened for TB; 25 percent of them had positive reactions. The county health department was notified and attempts are being made to find those persons with the active disease.

Follow-up medical care is generally coordinated through a school nurse, county health department, rural health clinic or a private physician. Dr. Tidwell rates follow-up "fair to good, so far. We are trying very desperately to keep a good follow-up system going, and we may have to hire an additional RN to do follow-up. Of course we'd like to see local county medical societies get involved in caring for these children," he said. "We would like physicians to say 'we have an obligation to all people, regardless of nationality, and that if there are poor people in our community we have a duty to take care of them.'

"We do hope to refer more children to local physicians for treatment, because we are really there primarily to do screening. We realize this referral will be predicated on the local physician's ability to absorb more patients and the availability of funds to pay for needed care."

Sheer numbers dictate that the health team probably will continue to confine itself to initial screenings and examinations. Dr. Tidwell says there are an estimated 18,000 migrant children in the state of Washington during a year and that Washington attracts more migrants than any other single state. He added that the moves of migrants are well documented and that those coming to this state are mostly from Texas. They begin to arrive in mid-March for the asparagus harvest and many stay through October when apples are picked. Although most migrants are Chicanos, Canadian Indians have been migrating to Western Washington for several generations to pick berry crops.

Bea Smith, pediatric nurse practitioner, examines child in Bainbridge Island migrant health program.

While Dr. Tidwell believes the pilot project demonstrated that health care can be delivered to migrants, he identifies "time" as the biggest problem the project faces. "I mean time in terms of money, manpower and facilities," he said. "There's no way we can ever see these children as frequently as any child on welfare is seen."

Future plans for the project call for an educational program to improve the general health status of migrant children over the long-term; nutrition, sanitation and preventive care will be particularly stressed.

A handbook is in production on the logistics of the program and the kinds of personnel involved. The handbook is expected to serve as a guide to other states with sizable migrant populations with unmet health needs.

Physicians interested in further information on the migrant health project should contact Dr. Tidwell at 1001 Broadway, Seattle 98122 (telephone 206-329-5868).

'Fun Run' at Annual Meeting

For relaxation during the WSMA annual meeting, a physicians' "Fun Run" will be held, along with golf and tennis tournaments. The run will take place Saturday morning, October 6, along the waterfront north of downtown Seattle. Both the golf and tennis tournaments will take place on Thursday, October 4; tennis will be played at Tennis World and golf will be at the Broadmoor Golf Club. Details on registration and exact times of these events will be published in the annual meeting packet to be mailed in mid-August.

Rubella Prevention a 'Must' for Women of Child Bearing Age

By Donald A. Sutherland, M.D.
Chairman, WSMA Maternal and Infant Health Committee

Rubella, a common viral childhood illness with rash, is frequently overlooked or misdiagnosed because of its varied and mild symptoms. This same mild childhood disease can be devastating when it infects a pregnant woman because it can cause major single or multiple congenital malformations in the fetus. The incidence of fetal involvement with maternal infection has been estimated to be as high as 33% in the first month of gestation—a particularly formative time for the developing fetus. By far the most important consequences of rubella are these fetal anomalies. Thus, *any control program should consider how to prevent rubella in women of child bearing age.*

In the new immunization rules and regulations for school children in Washington state, rubella vaccine will be required of all students except females 12 years of age or older. It is hoped that many of these girls in this older age group will have already been immunized. The exclusion of this age group from mass immunization is based on the possibility of vaccinating the young girl who is, or who may become pregnant within three months of vaccination. The exclusion, however, does not resolve the problem of the most vulnerable group—the girls who may become infected while pregnant and who may deliver a child with major congenital anomalies.

Protection of women of child bearing age against exposure to rubella has been discussed in several recent publications.

In the Center for Disease Control *Morbidity and Mortality Weekly Report* of April 14, 1978, the editors said, "Ideally all women of child bearing age should be tested for immunity to rubella. If found susceptible, they should be offered immunization against rubella, following routine precautions to ensure that they are not pregnant and will not become pregnant for three months following immunizations."

Dr. Lawrence Bergner, director of the Seattle-King County Health Department, wrote to King County hospital administrators on May 31, 1978, about the problem of protecting women of child bearing age. He said, "We assume, except in those facilities which screen staff in contact with pregnant women for rubella susceptibility and vaccinate the susceptibles, that the risk of exposing pregnant and potentially pregnant women to rubella, through an outbreak among personnel exists in medical care settings. . . We urge hospitals not already doing so, to undertake such a screening and vaccinating program in their facilities for personnel (male and female) in close contact with pregnant women."

Recommendations of the Public Health Service Advisory Committee on Immunization Practices, reported in the November 17, 1978, CDC *Morbidity and Mortality Weekly Report*, include: "Educational and training institutions such as colleges, universities and military bases should seek proof of rubella immunity (a positive serologic test or documentation of previous rubella vaccination) from all female students and employees of child bearing age. Nonpregnant females who lack proof of immunity should be vaccinated unless contraindications exist.

"In order to protect susceptible female patients and female employees, persons working in hospitals and clinics who might contract rubella from infected patients, or who, if infected, might transmit rubella to pregnant patients should be immune to rubella."

The entire problem of rubella prevention is well reviewed by Dr. John Taylor, state epidemiologist, in the DSHS Communicable Disease Report, January, 1979.

In spite of the new mandatory immunization law, the potential still exists for rubella exposure to pregnant women and the subsequent devastating effects to the fetus. The WSMA Maternal and Infant Health Committee urges all physicians to review their immunization practices and to take steps to fill any gaps. We urge you to act now. Too late is too late.

"I shall pass through this world but once. Any good, therefore, that I can do, or any kindness that I can show to any human being, let me do it now. Let me not defer nor neglect it, for I shall not pass this way again."—Author unknown.

References on rubella and general immunization guidelines are—

(1) Center for Disease Control Morbidity and Mortality Weekly Report: April 14, 1978, Volume 27, Number 15
(2) Letter from Dr. Lawrence Bergner, M.P.H., Seattle-King County Department of Public Health: "To Hospital Admininstrator," May 31, 1978
(3) Center for Disease Control Morbidity and Mortality Weekly Report: November 17, 1978, Volume 27, Number 46
(4) Communicable Disease Report: Washington State Health Services Division, January, 1979
(5) Report of the Committee on Infectious Diseases, American Academy of Pediatrics, Eighteen Edition, 1977
(6) "Why Your Children Need Immunization": State of Washington Department of Social and Health Services, Revised 1977

Medical Care for Children Featured

Scientific Sessions Offered at WSMA Annual Meeting

In recognition of the International Year of the Child, medical care for children will receive considerable emphasis in the Scientific Program during the WSMA Annual Meeting, October 4–7 at the Washington Plaza Hotel, Seattle. Both Category I and Category II CME credits will be offered for attendance at scientific sessions. AAFP prescribed credits have been approved on a credit per hour basis.

The WSMA Scientific Program Committee, composed of 13 physicians representing diverse specialties, developed the scientific sessions. Scientific sessions will be held October 5 and 6.

Complete details on the annual meeting will be mailed to WSMA members in mid-August, and other physicians may obtain a copy of the preliminary program by writing to the WSMA Central Office. Registration fee for physicians who are not WSMA members is $50.

The following scientific programs will be offered during the meeting:

Friday, October 5

PEDIATRICS

Year of the Child
Pediatric Tuberculosis

INTERNAL MEDICINE

Oncology: Progress in the 70's

The Lymphomas
Lung Cancer
Breast Cancer

Workshops—Case Discussions

Childhood Malignancies
Lung Cancer
Breast Cancer
Lymphomas/Leukemias
Unapproved Methods of Cancer Therapy

RADIOLOGY/NUCLEAR MEDICINE

Clinical Application of Abdominal Ultrasonography, C.T. and Nuclear Medicine
Recent Advances of C.T. in Head, Thorax, and Skeleton
Recent Advances in Perinatal Ultrasonography
Pediatric Nuclear Medicine
Pot Pourri in Pediatric Radiology

PSYCHIATRY

Overview of Field of Psychosomatic Medicine, Psychological Influences on Medical Disease and Psychobiology
Psychological Influences on the Immune Systems
Psychological Factors in Gastro-Intestinal Illness
Psychological Influences on Cardiovascular Illness (Coronary artery spasm, hypotension and sudden death)
Psychological Influences on Cardiovascular Illness
Quality of Life: Psychological Factors in the Treatment and Rehabilitation of the Cancer Patient

SURGERY

Hypothermia for Children
Management of the Burned Child
Management of Childhood Athletic Injuries
Trauma in Children

Surgical Diagnostic Pitfalls
- Ultrasound and Pancreatic Masses
- Ultrasound and Gall Stones—With or Without Cholangiograms
- Skinny Needle Cholangiograms
- Cancers in the Normal Mammograms
- Mole or Melanoma
- The Fiberoptic Sigmoidoscope
- Failure of Intestinal Bypass for Morbid Obesity
- Tricks with the Doppler: Carotid, Veins, and Arteries

EMERGENCY MEDICINE

Unusual But Urgent Infectious Diseases
Iatrogenic Difficulties with Drugs
Saturday Night Fever
Acute Allergic Reactions

Saturday, October 6

OPHTHALMOLOGY

Two New Surgical Instruments
Automated Refraction
Secondary Retinal Detachments and Subretinal Neovascular Membranes
Acquired Hyperopia with Choroidal Folds
Homonymous Hemianopsia Associated with Coronary Artery Bypass Surgery
Adjustable Eye Muscle Sutures under General Anesthesia
Traction Retinal Detachments
Trabeculectomy in Aphakia
Idiopathic Retinal Dialysis
A Better Eye Patch
Ocular Findings that Provide Key Information for Genetic Counseling in Systemic Diseases
Ophthalmic Findings in Sotos Syndrome: An Example of the Importance of Ocular Findings in Systemic Genetic Diseases
An Ophthalmologist's Perspective of Dyslexia
Optic Neuritis and Retrobulbar Neuritis and Devic's Disease in Children
Sex, Pregnancy and Red Eyes: An Updated View of Ophthalmia Neonatorum

INTERNAL MEDICINE

Hairy Cell Leukemia
Immunology of Cancer/Progress in Experimental Immunotherapy
Testicular Cancers
Marrow Transplantation in Malignancy

(cont'd on p. 8)

Saturday, October 6
Scientific Sessions Cont'd.

ALLERGY AND IMMUNOLOGY

Bee Sting Allergy
Historical Aspects of Hymenoptera Allergy
Current Research and Therapy of Hymenoptera Allergy
Chronic Lung Disease in Children
Update in the Use of Theophyllines
Update in the Use of Adrenergic Bronchodilators
Update in the Use of Steroids
New Drugs in Research

ANESTHESIOLOGY

The Impact of Consumerism on Childbirth: Medical Care or a Social Affair
Anesthetic Considerations for Mother and Infant in High Risk Obstetrics
Local Anesthetic Agents and Newborn Neurobehavioral Changes
Resuscitation and Transport of the High Risk Infant

PSYCHIATRY

Family Diagnosis and Family Therapy: New Perspectives on Psychosomatic Illness in Children
The Effects of Premature Ingestants (Alcohol and Other Substances) and Their Effect on Child Development
Influences of Injury, Chronic Illness and Disability on Personality Development in Childhood
Psychosocial Stresses on the Preschool and School-Age Child: Television Violence and Commercials, Schools, Working Mothers, Daycare, Etc.

CURRENT INTERVIEWING, DIAGNOSTIC AND MANAGEMENT TECHNIQUES WITH THE PSYCHIATRIC PATIENT

(This Seminar will be repeated four times through October 5 and 6.)

(Editorial cont'd from p. 1)

However, the informed physician-manager is the best instrument to balance the Art and Science of Medicine, and the competing accountability to the patient and to the public—compassionate, yet objective, intuitive, yet scientific, and where it is useful even mystical.

But management without good management information is likely to be bad management. The physician is deluged by a flood of diagnostic and therapeutic choices that muddy the Art and erode the Science of Medicine. Technology assessment can provide the opportunity for informed choices and more skillful patient management.

The promise of a font of enlightened all-wise choice is certainly seductive; and here lies a *caveat*. The bias, flawed judgments and incentives of the assessors may be substituted for the bias, flawed judgment and incentives of the practitioners. Who will assess the assessors? Or does hallowed academic stature in some Institute or University toward the East confer infallibility? Technology assessment is neither a pure nor hallowed science, it is where the grants are, where there are papers to be written, reputations to be made, and philosophical and political goals to be advocated. As a measure of fallibility I suggest a test. Name the political party of choice of the proponents and opponents of (a) the UGDP study condemning the oral antidiabetic agents; (b) a Think Tank study advocating the building of the B-l bomber; (c) the V.A. study questioning the usefulness of coronary artery bypass surgery; (d) the Mancuso report highlighting the health hazards of nuclear power generation.

However, one should not impugn the motives of technology assessors any more than those of practitioners, most of whom are honorable scientists seeking diagnostic and therapeutic truth in the management of their patients.

The questionmark in the title is neither to praise nor to damn technology assessment. It only suggests there is no unquestioned wisdom, that the most elegant paper should be tested by common sense and practitioner observations.

The technology of technology assessment needs to be advanced to make all of us practitioners better scientists, evaluating better the gold mine of our own experience. How many times have you wanted to review your own cases of "whatever itis" and couldn't retrieve more than your nurse could remember. The technology is available today, but not the commitment. Bjorne & Cross have applied a technique of case retrieval and study for their own offices. Hospital department audits are technology assessments in our own backyard, attuned to the demography of our own patients and to our own skills, susceptible to our evaluation of the competence and motives of the assessors. WSPRO, an organization of some of our best physicians, has an enormous capability for technology assessment, if we can resolve the problem of patient confidentiality. Blue Shield plans — the Doctors' plans—with imagination and commitment, plus their computer capability, have for years forfeited a marvelous opportunity for technology assessment. Judgments made from an evaluation of our own experience would be more useful than observations from the Great Center with their own often skewed patient demography, and have the virtue of simultaneous consensus development and technology transfer.

This is no doleful, xenophobic diatribe, rather an optimistic exhortation to practitioners to pursue the Science as well as the Art of Medicine, as informed physician-managers. We are sworn to the Art, let us profess the Science.

Alvin J. Thompson, M.D.
Chairman, WSMA Executive Committee

THE WESTERN
Journal of Medicine

Refer to: Heffner JE: Extracardiac manifestations of bacterial endocarditis. West J Med 131:85-91, Aug 1979

Extracardiac Manifestations of Bacterial Endocarditis

JOHN E. HEFFNER, MD, *Oceanside, California*

Bacterial endocarditis is an elusive disease that challenges clinicians' diagnostic capabilities. Because it can present with various combinations of extravalvular signs and symptoms, the underlying primary disease can go unnoticed.

A review of the various extracardiac manifestations of bacterial endocarditis suggests three main patterns by which the valvular infection can be obscured. (1) A major clinical event may be so dramatic that subtle evidence of endocarditis is overlooked. The rupture of a mycotic aneurysm may simulate a subarachnoid hemorrhage from a congenital aneurysm. (2) The symptoms of bacterial endocarditis may be constitutional complaints easily attributable to a routine, trivial illness. Symptoms of low-grade fever, myalgias, back pain and anorexia may mimic a viral syndrome. (3) Endocarditis poses a difficult diagnostic dilemma when it generates constellations of findings that are classic for other disorders. Complaints of arthritis and arthralgias accompanied by hematuria and antinuclear antibody may suggest systemic lupus erythematosus; a renal biopsy study showing diffuse proliferative glomerulonephritis may support this diagnosis. The combination of fever, petechiae, altered mental status, thrombocytopenia, azotemia and anemia may promote the diagnosis of thrombotic thrombocytopenic purpura.

When the protean guises of bacterial endocarditis create these clinical difficulties, errors in diagnosis occur and appropriate therapy is delayed. Keen awareness of the varied disease presentations will improve success in managing endocarditis by fostering rapid diagnosis and prompt therapy.

BACTERIAL ENDOCARDITIS is an elusive disease. Protean systemic manifestations and the latency of cardiac symptoms often combine to obscure the presence of valvular infection. A common error in diagnosis occurs when an extracardiac complication of endocarditis is mistaken for a separate disorder. A cutaneous vasculitis, a migratory polyarthralgia or a ruptured cerebral aneurysm may appear to be a primary disease when evidence of cardiac involvement is subtle. The consequent delay of correct evaluation decreases

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Submitted, revised, February 7, 1979.

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ABBREVIATIONS USED IN TEXT

ANA = antinuclear antibody
DIC = disseminated intravascular coagulation
SBE = subacute bacterial endocarditis

the probability of a successful outcome to antibiotic therapy.

This paper reviews the characteristic extracardiac manifestations of bacterial endocarditis. Emphasis is placed on the clinical complications and laboratory signs which should suggest endocarditis in difficult instances in which little direct evidence of valvular infection exists.

Immunological Manifestations

In patients with bacterial endocarditis, a polyclonal immunological response to foreign proteins develops. A number of autoantibodies and exoantibodies develop of which only 15 percent have specificity for the invading organism.[1]

There are several manifestations of this heightened immunological state. Rheumatoid factor has been found in 24 percent to 50 percent of patients with subacute bacterial endocarditis (SBE)[2-5] and can occur in titers as high as 1:5,120.[2] It tends to develop in patients with long duration of disease.[6] If endocarditis has been present for six weeks, 50 percent of patients have positive test results for rheumatoid factor, while only 6 percent have positive results if disease has been present for less than six weeks.[4] There is no correlation with type of infecting organism[5,6] or with degree of immune complex elevation.[7] Apparently, continuous antigenic exposure versus intermittent stimulation is necessary since drug abusers with staphylococcal endocarditis have a 24 percent incidence of rheumatoid factor, while only 7 percent of noninfected abusers who intermittently inject antigen were found to have measurable levels.[4] After the initiation of antibiotic therapy, titers may immediately decline and become negative in six to eight months.[4,5]

Cryoglobulinemia of the mixed type has a prevalence of 90 percent in SBE. The degree of elevation tends to parallel the course of the disease but does not prognosticate or appear to be higher in patients with nephritis.[8]

Circulating immune complexes assayed by the Raji method are found in endocarditis.[7,9] In one study, 97 percent of patients with SBE had levels greater than 12 μg per ml, while this level was found in 32 percent of patients with sepsis, 40 percent of drug addicts and 10 percent of normal controls. Levels greater than 100 μg per ml were not found in any patient without endocarditis and occurred in 35 percent of the SBE group. This degree of elevation correlated with duration of disease and extravalvular signs such as splenomegaly, arthralgia-arthritis, Roth spots, nephritis and thrombocytopenia. All patients whose cases are followed serially have a fall in immune complex levels with successful therapy. Persistent elevations may foretell treatment failure.[7]

Measurements made early in the course of endocarditis show serum complement to be variably elevated,[1] normal[2] or low[7] in patients without nephritis. However, if complement is followed serially during therapy there is generally a rise in titer and any initial depression corresponds inversely to the elevation of circulating immune complexes.[7] Patients with nephritis uniformly have total complement depression,[2,10-12] which responds to antibiotic therapy.[12]

As would be expected in endocarditis with its broad nonspecific hyperimmune state, other antibodies have been noted. Results of tests for antinuclear antibody (ANA) are positive in 8 percent to 30 percent of SBE patients, with titers as high as 1:640. Positive ANA test results revert to negative after antibiotic therapy.[1-3,9,12] Also occurring are antiheart antibody;[3] positive tests for syphilis (Venereal Disease Research Laboratory);[3] antibody against Candida albicans,[1] and several other organ-specific antibodies: smooth muscle antibody,[1-9] mitochondrial antibody,[1,9] thyroidal antibody, gastric parietal cell antibody and skeletal muscle antibody.[1]

Cutaneous Manifestations

Probably no sign of endocarditis is as widely advertised, yet is of as little value as subungual splinter hemorrhages. The specificity of this sign for endocarditis is very low. Of all patients admitted to hospital, 10 percent to 66 percent have splinter hemorrhages,[13,14] with highest incidences in patients with mitral stenosis without endocarditis[15] and in those in whom hemodialysis[16] or peritoneal dialysis is being carried out.[14] Because this finding is noted in only 12 percent of patients with SBE,[17] it provides little diagnostic value as an isolated finding. The finding is important for patients with known or suspected endocarditis in whom splinter hemorrhages develop

during in-hospital observation, thereby providing evidence for ongoing disease.[18]

Osler nodes, which occur in endocarditis, are painful nodes similar to wheals that develop most often on the pads of the fingers and toes or on the palms and soles. Always erythematous with slightly white centers, they differ from Janeway lesions in their tenderness and lack of hemorrhage. They have been reported in systemic lupus erythematosus,[19] typhoid fever, gonorrhea, marantic endocarditis, as well as acute[20] and subacute endocarditis. In the preantibiotic era, their frequency was 50 percent to 70 percent, but they now occur in 10 percent to 23 percent of cases.[18] However, when present they may be a chief complaint,[17] suggesting the diagnosis of endocarditis or allowing early identification of organisms on Gram stain.[21]

The pathogenesis of Osler nodes is not yet settled. Osler felt they were "in all probability caused by minute emboli."[22] Biopsy reports[23] showing necrotizing vasculitis of the dermal glomus with sparing of the dermal vessels, along with burgeoning evidence that many other complications of endocarditis are immune related, have led some to conclude that Osler nodes are inflammation from immune complexes settling into tissue.[9] However, these biopsy specimens were generally taken after the lesions had been present for ten days. When earlier specimens are examined, microabscesses have been seen[24] and organisms cultured[20,21,24] or observed on Gram stain.[21,24] These results suggest that the perivasculitis may be a local response to a septic embolus rather than a reaction to a diffuse immunological event. This view fits the observations that Osler nodes occur preferentially in the distal circulation and that they are rare compared with other immunological complications such as nephritis.

Petechiae remain one of the most common signs of endocarditis; they occurred in 85 percent of patients in the preantibiotic era and occur in 19 percent to 50 percent now.[18] They do not blanche, and they occur most commonly around the clavicle, lower neck, conjunctivae, and hard or soft palate. They appear in waves and crops, lasting a few days before fading into brown spots.

In endocarditis, petechiae rarely progress to generalized purpura.[25-30] In staphylococcal endocarditis, purpuric lesions may progress into cutaneous gangrene[28,29] or may be pustular, with organisms present on Gram stain.[29,30] Pathological sections show intravascular thrombosis, focal necrosis of vessel walls, extravasation of erythrocytes[26] and IgM deposition in the dermoepidermal junction.[31] Platelet counts may be normal[25] or depressed,[29,30] and clotting studies either give normal findings[25] or results consistent with disseminated intravascular thrombosis.[29,32] The clinical pattern of acute meningococcemia[29] or leukocytoclastic vasculitis[27] may be mimicked when endocarditis presents with generalized purpura.

Nail clubbing has long been a hallmark of subacute endocarditis; it occurred in 76 percent of cases in older series and occurs in 12 percent to 52 percent in the antibiotic era.[18] Rarely, it can be associated with hypertrophic osteoarthropathy.[33]

Splenic Manifestations

Splenomegaly occurs in 23 percent to 57 percent of endocarditis patients.[18] Spleens as large as 1,400 grams[34] are sometimes the major mode of presentation, suggesting an underlying lymphoreticular disease. Splenic infarctions resulting from arterial emboli are the greatest cause of splenomegaly[24] and are found in 40 percent to 60 percent of autopsies done in cases of endocarditis.[18,35,36] Splenic infarcts are seldom symptomatic; but they can generate severe left upper quadrant pain, local rebound, the Kehr sign, pleuritic pain and a friction rub.[34] The pain of splenic infarction may be the presenting complaint in 5 percent of patients and can lead to a diagnosis of pulmonary embolus, pneumonia or a primary intraabdominal event. A spleen scan may give positive results, showing a defect if the infarct is large enough.[37]

Although the infarcts are due to infected emboli, the low virulence of the organisms usually results in a nonsuppurative lesion; splenic abscesses rarely develop. In the preantibiotic era, 10 percent of patients who died of endocarditis had suppurative foci in the spleen; since the introduction of antibiotics, only a few cases have been reported.[38-40]

Splenic rupture rarely occurs in endocarditis; but, when present, it is a particularly lethal complication. Rupture may be the first manifestation of disease, or it may occur after the endocarditis has been bacteriologically cured.[36]

Pulmonary Manifestations

X-ray studies of the chest in cases of left-sided endocarditis are generally not revealing in the

absence of congestive heart failure. Pulmonary manifestations are due to right-sided cardiac infection or left-sided involvement with a left-to-right shunt;[41,42] most often they occur in intravenous drug abusers or in immunosuppressed patients.[41] Tricuspid infection is common in these persons; with or without other valve involvement, endocarditis occurs on the tricuspid valve in 72 percent of heroin addicts with endocarditis, and pulmonary disease may be the major presenting feature in 66 percent.[41,43] The clinical features are fairly uniform: There is usually no previous heart disease and minimal evidence for a cardiac disorder; pulmonary dysfunction is the apparent primary problem with chest pain, cough and shortness of breath as the most common chief complaints.[41] An x-ray film of the chest may show pneumonia demonstrated by cavitary or multiple alveolar infiltrates, pulmonary emboli in 10 percent to 38 percent,[43] empyema, pneumothorax, lung abscess, pleural effusions and pulmonary artery mycotic aneurysms. The valvular infection may go unnoticed because a cardiac murmur is absent in 45 percent of patients if pulmonary complications occur.[43] Staphylococcus aureus is the most common organism in this setting,[43-45] and mortality is low with early diagnosis and aggressive therapy.

Neurological Manifestations

Neurological complications of bacterial endocarditis present diversely and closely mimic primary central nervous system processes. Between 15 percent and 50 percent of patients will have neurological complaints during the course of disease,[34,46-48] and these complaints will be the major presenting problems in 6 percent to 28 percent.[47] The incidence of neurological manifestations is the same in subacute and acute endocarditis, and the frequency has not decreased with the development of antibiotics.[47,48] Mortality is only marginally increased in groups of patients in whom general neurological complaints develop,[46] but it is significantly higher if a major complication such as a stroke, delirium or coma occurs.[17]

Major emboli to the central nervous system occur in 30 percent to 50 percent of patients with subacute endocarditis;[18,35,48] and, conversely, 3 percent of all emboli to the head originate in infected valves.[18] The emboli most commonly lodge in the middle cerebral artery, producing hemiplegia and parietal signs.[18,46] However, essentially any arterial watershed is in jeopardy, and any constellation of ischemic neurological signs can develop. Emboli to the spinal cord are rare but can produce girdle pain or paraplegia.[18]

Embolic episodes are not limited to the period of active valve inflammation and can be manifest months to years after a bacteriological cure.[18,41,47,49] Cates and Christie observed an 11 percent incidence of cerebral emboli with an 80 percent early mortality in patients without atrial fibrillation occurring one to 70 days after cessation of antibiotic therapy.[49] The higher mortality of late emboli as compared with early emboli suggests that healed vegetations present a greater threat since they are fibrosed and calcified with resultant emboli that are larger and less likely to break up in the intracranial arterial circulation than are the friable particles embolized during active valvular inflammation. Valve replacement or debridement[5] is warranted for recurrent emboli.

Occult endocarditis may present as aseptic or purulent meningitis. Aseptic meningitis is much more common than the purulent form in subacute endocarditis.[18,47,48] The resulting meningoencephalitis may be severe, with nuchal rigidity and an acute brain syndrome. Analysis of cerebrospinal fluid commonly shows no organisms on smear or culture, fewer than 500 leukocytes per cu mm most of which are mononuclear, elevated protein value and normal glucose value.[48] The meningeal findings usually are transient and resolve completely whether or not the patient receives antibiotics.

Acute suppurative meningitis is a complication of acute, usually staphylococcal,[46] endocarditis and is the most common neurological presentation of endocarditis with this organism.[2] When S. aureus is involved, the cerebrospinal fluid findings are often nonspecific: The leukocyte count is generally less than 1,000 per cu mm with a predominance of polymorphonuclear cells; the protein value is elevated; the glucose value is usually normal, and cultures or smears are positive in only 20 percent of instances.[51]

Brain abscesses are rare in SBE (1 percent of cases) but are found in 24 percent of cases of acute endocarditis, usually as small multiple abscesses.[47,48] They may present as sterile meningitis, intracranial mass lesions or a toxic encephalopathy.[47] Generally, drainage procedures are ineffective because the lesions are small and are often multiple.[18,35,48]

Intracranial mycotic aneurysms complicate bacterial endocarditis in 2 percent to 18 percent of

instances[17,18,47,52] and are more frequent with noninvasive organisms than with S. aureus which usually promotes abscess formation.[18,48] However, mycotic aneurysms are sufficiently common in acute endocarditis that diagnostic procedures are warranted if the clinical findings are even slightly suggestive of an aneurysm.[17,53] The actual incidence in all forms of endocarditis may be higher; cerebral angiography is not done in all patients, and many may remain asymptomatic. Of all intracranial aneurysms in general patient populations, 2.5 percent to 4 percent are mycotic.[54] They usually occur singly, but they can be multiple; they are most frequently found along the middle cerebral artery, although any artery is subject to them.[18,47] They differ from congenital aneurysms by being more peripheral beyond the first bifurcation and are less often in the anterior circulation,[18] but exceptions do occur.[55]

The importance of mycotic aneurysms is greater than their frequency would suggest; often the first sign of their existence is a fatal intracranial hemorrhage. Rupture, which carries a 60 percent to 90 percent mortality,[47] may be prevented in some cases with early diagnosis, close observation and surgical intervention when possible. The unpredictability of outcome is pronounced: fatal rupture may occur one to 22 months after the cessation of administration of antibiotics and bacteriological cure.[17,54]

Premorbid symptoms of a mycotic aneurysm do occur, but more frequently the aneurysm ruptures unexpectedly. The symptoms of impending rupture are the same as those seen with cerebral aneurysms resulting from other causes.

Once established, aneurysms have variable natural histories. They may rupture early or late, may persist unchanged except for wall calcifications, may thrombose and decrease in size or may resolve with complete disappearance in possibly half of the cases.[56-58]

Four-vessel cerebral angiography is required to show the existence of a mycotic aneurysm. There are no reports of success in utilizing computerized tomography. Because of the potential lethality, an aggressive approach should be adopted for prompt diagnosis in certain situations. Any patient with endocarditis in whom there is sterile meningitis with focal neurological signs or unilateral headache, or both[59] or a patient with endocarditis and a subarachnoid hemorrhage[55] should have an angiographic study. Once the aneurysm is diagnosed in an initial arteriogram, the lesion should be followed every two to three weeks by repeat studies to check on size and look for new aneurysmal development. Preferably, surgical operation should be postponed until after a complete course of antibiotics because in the inflamed state the aneurysm is friable and the parent artery is necessarily sacrificed. With healing, the aneurysm wall fibroses, allowing placement of a clip.[60] However, if leaking has occurred and if the lesion lies peripherally, arterial ligation preferably should be done early rather than risk complete rupture. Otherwise, the aneurysm should be followed and surgical operation should be done without delay if it is larger on the first follow-up study, or if it is the same size or larger after a complete course of antibiotics.[56]

Psychiatric manifestations occur in up to 50 percent of patients with endocarditis.[47] Hallucinations, confabulation, depression, paranoid ideation, fluctuating confusion and impaired concentration commonly develop, particularly in elderly patients. Endocarditis should always be considered in any unexplained sudden personality change in an older person.

Major retinal complications of endocarditis include hemorrhage, cotton wool patches and a peculiar retinal hemorrhage with a pale center that is erroneously termed a Roth spot.[18,34] Roth, in 1872, described hemorrhages and cotton wool patches in cases of sepsis, terming them septic retinitis; but he did not link them to endocarditis nor did he note the lesion carrying his name.[61] Litten, in 1876, observed the association of endocarditis with retinal hemorrhages containing pale centers and called them Roth spots.[62] This lesion is probably due to a focal accumulation of leukocytes and the cotton wool patches are cytoid bodies.[63] Neither are specific for endocarditis.

Hematologic Manifestations

The leukocyte count is usually normal in patients with S. viridans endocarditis.[35] Leukocytosis in a patient with endocarditis suggests embolic or suppurative complications or a more virulent organism than S. viridans. The circulating polymorphonuclear leukocytes appear to have an acquired intracellular killing defect when compared with those of patients with other forms of acute bacterial infections or of persons used as controls.[64] This defect resolves with the initiation of antibiotic therapy.

Thrombocytopenia with platelet counts as low

as 3,000 to 5,000 per cu mm can occur in SBE,[51,65] and counts under 100,000 per cu mm may be as frequent as 34 percent to 39 percent.[29] The symptom complex of endocarditis with fever, renal insufficiency, neurological manifestations and anemia may suggest a diagnosis of thrombotic thrombocytopenic purpura.[26,66] The bone marrow in instances of thrombocytopenia is normal, showing normal or increased number of megakaryocytes.[29,51,66] Circulating immune complexes are highest at the platelet nadir and decrease when the platelet count returns to normal.[64,66]

Of patients with endocarditis, 75 percent have an anemia.[67] Most commonly, anemia of chronic infection with normocytic normochromic red cells exists but splenomegaly may cause a hemolytic anemia through sequestration,[68] or occasionally a deformed valve may promote intravascular hemolysis.[66]

Coagulopathies are not common associates of Gram-positive infections but the occurrence of disseminated intravascular coagulation (DIC) in S. aureus endocarditis may be more common than suspected.[29,32] In two series of cases of staphylococcal sepsis in which coagulation profiles were attained, the incidence of DIC was 15 percent.[69,70]

Musculoskeletal Manifestations

Musculoskeletal manifestations of endocarditis occur in 17 percent to 50 percent of patients and usually develop early in the course of the disease.[71] Arthralgias and arthritis are the most common complaints and most frequently involve the large joints of the lower extremities.[71] They are fleeting in nature and can affect several joints in an asymmetrical pattern; however, a symmetrical polyarthritis may mimic a collagen vascular disease.[74]

The synovitis is almost uniformly sterile with only rare instances of positive findings on cultures of synovial fluid.[72] Analysis of synovial fluid is not revealing, with 1,200 to 16,500 leukocytes per cu mm with variable predominance of polymorphonuclear cells, negative cultures, negative latex agglutination, normal complement and nonspecific biopsy results showing acute inflammation.[73] The arthritis resolves with antibiotic treatment of the endocarditis.

Other manifestations include myalgias,[71] severe back pain,[71,75] disc space infections,[71] and hypertrophic osteoarthropathy.[33] The cause of the musculoskeletal complaints is probably immune mediated. The common occurrence of monoarticular complaints suggests that a generalized immune complex process does not play a role but rather that an embolus laden with antigen lodges in a periarticular area and initiates a localized immunologic event.[71]

Renal Manifestations

Endocarditis commonly initiates an active urinary sediment with red cells, leukocytes, proteinuria and red-cell casts. Three forms of renal involvement are recognized in endocarditis: (1) infarctions of portions of the kidney from large arterial emboli,[65] which are found in 56 percent of autopsies done in cases of endocarditis;[18] (2) focal glomerulonephritis, which probably is due to either small emboli[12,65] or immune complexes,[11,76] and (3) diffuse glomerulonephritis, which is an immune complex nephritis.[12] Of the three forms, the only one that causes renal insufficiency is the diffuse glomerulonephritis.[12,34]

Renal infarction is usually asymptomatic; but when it is present, flank pain is the major symptom, with hematuria and pyuria.[41] The histology of the immune complex nephritis is the "lumpy bumpy" type of immunofluorescence[12] and is not specific for endocarditis.[65] Deposits of C3 and immunoglobulins are found in the glomerular tufts[10-12] along with bacterial antigen[10] and antibody specific for the invading organism.[77] Electron dense deposits are noted on electronmicroscopy,[12] and peripheral serum complement is depressed.[10-12] Renal histology and function generally improve with antibiotic therapy for the endocarditis.[10]

REFERENCES

1. Bacon PA, Davidson C, Smith B: Antibodies to Candida and autoantibodies in subacute bacterial endocarditis. Q J Med 43:537-550, 1974

2. Lerner P, Weinstein L: Infective endocarditis in the antibiotic era. N Engl J Med 274:199-206, 259-266, 323-331, 388-393, 1966

3. Das SK, Cassidy JT: Importance of heart antibody in infective endocarditis. Arch Intern Med 137:591-593, 1977

4. Sheagren JN, Tuazon CU, Griffen C, et al: Rheumatoid factor in acute bacterial endocarditis. Arthritis Rheum 19:887-890, 1976

5. Williams RC, Kunkel HG: Rheumatoid factor, complement, and conglutinin aberrations in patients with subacute bacterial endocarditis. J Clin Invest 41:666-675, 1962

6. Messner RP, Laxdal T, Quie PD, et al: Rheumatoid factors in subacute bacterial endocarditis—Bacterium, duration of disease or genetic predisposition? Ann Intern Med 8:746-756, 1968

7. Bayer AS, Theofilopoulous AN, Eisenberg R, et al: Circulating immune complexes in infective endocarditis. N Engl J Med 295:1500-1505, 1976

8. Hurwitz D, Quismario FP, Friou GJ: Cryoglobulinemia in patients with infective endocarditis. Clin Exp Immunol 19:131-141, 1975

9. Mohammed I, Ansel BM, Holborrow EJ, et al: Circulating immune complexes in subacute bacterial endocarditis and post-streptococcal glomerulonephritis. J Clin Pathol 30:308-311, 1977

10. Perez GO, Rothfield N, Williams RC: Immune-complex nephritis in bacterial endocarditis. Arch Intern Med 136:334-336, 1976

11. Boulton-Jones JM, Sissons J, Evans D, et al: Renal lesions of subacute infective endocarditis. Br Med J 2:11-14, 1974

12. Gutman RA, Striker GE, Gilliland BC, et al: The immune complex glomerulonephritis of bacterial endocarditis. Medicine (Baltimore) 51:1-26, 1972

13. Robertson JC, Broune ML: Splinter hemorrhages, pitting and other findings in fingernails of healthy adults. Br Med J 4: 279-281, 1974

14. Kilpatrick ZM, Greenberg PA, Sanford JP: Splinter hemorrhages—Their clinical significance. Arch Intern Med 115:730-735, 1965

15. Platts MM, Greaves MS: Splinter hemorrhages. Br Med J 2:143-144, 1958

16. Blum M, Aviram A: Splinter hemorrhages in patients receiving regular hemodialysis. JAMA 239:47, 1978

17. Pelletier L: Infective endocarditis—A review of 125 cases from the University of Washington Hospitals, 1963-1972. Medicine (Baltimore) 56:287-313, 1977

18. Weinstein L, Rubin RH: Infective endocarditis—1973. Prog Cardiovasc Dis 16:239-274, 1973

19. RuDusky BM: Recurrent Osler's nodes in systemic lupus erythematosus. Angiology 20:33-37, 1969

20. Puklin JE, Balis GA, Bentley DW: Culture of an Osler's node—A diagnostic tool. Arch Intern Med 127:296-298, 1971

21. Thadepalli H, Francis CK: Diagnostic clues in metastatic lesions of endocarditis in addicts. West J Med 128:1-5, 1978

22. Osler W: Chronic infectious endocarditis. Am J Med 2: 219-230, 1908-1909

23. Von Gemmingen GR, Winkeimann RJ: Osler's node of subacute bacterial endocarditis—Focal necrotizing vasculitis of the glomus body. Arch Dermatol 95:91-94, 1967

24. Alpert JS, Krous HF, Dalen JE, et al: Pathogenesis of Osler's nodes. Ann Intern Med 85:471-473, 1976

25. Horowitz LD, Silber R: Subacute bacterial endocarditis presenting as purpura. Arch Intern Med 120:483-486, 1967

26. Hall WH: Purpura fulminans with group B beta-hemolytic streptococcal endocarditis. Arch Intern Med 116:594-597, 1965

27. Lawrence EC, Mills J: Bacterial endocarditis mimicking vasculitis with steroid-induced remission. West J Med 124:333-334, 1976

28. Rahal JJ, MacMahon HE, Weinstein L: Thrombocytopenia and symmetrical peripheral gangrene associated with staphylococcal and streptococcal bacteremia. Ann Intern Med 69:35-43, 1968

29. Murray HW, Tuazon CU, Seagren JN: Staphyococcal septicemia and disseminated intravascular coagulation—*Staphylococcal aureus* endocarditis mimicking meningococcemia. Arch Intern Med 137:844-847, 1977

30. Plaut ME: Staphylococcal septicemia and pustular purpura—Report of cases. Arch Dermatol 99:82-85, 1969

31. Davis JA, Weisman MH, Dial DH: Vascular disease of infective endocarditis—Report of immune-mediated events in skin and brain. Arch Intern Med 138:480-483, 1978

32. Watanakunakorn C, Tan JS, Phair JP: Some salient features of *Staphylococcal aureus* endocarditis. Am J Med 54:473-481, 1973

33. McCord MC, Moberly J: Acute hypertrophic osteoarthopathy associated with subacute bacterial endocarditis. Ann Intern Med 39:640-644, 1953

34. Kerr A: Subacute Bacterial Endocarditis. Springfield, IL, Charles C Thomas, 1955

35. Weinstein L, Schlesinger JJ: Pathoanatomic, pathophysiologic and clinical correlations in endocarditis. N Engl J Med 291:832-836, 1122-1127, 1974

36. Vergne R, Selland B, Gobel FL, et al: Rupture of the spleen in infective endocarditis. Arch Intern Med 135:1265-1267, 1975

37. Spencer RP: Healing of a splenic infarct. J Nucl Med 15:303-304, 1974

38. Chulay JD, Lankerani MR: Splenic abscess. Am J Med 61:513-521, 1976

39. Schoenfeld MR, Messeloff CR, Han ST, et al: Large abscess of the heart and spleen complicating bacterial (enterococcal) endocarditis. Am Heart J 61:818-821, 1961

40. Gada LD: Changing clinical pattern of splenic abscess. Am J Surg 128:182-187, 1974

41. Garvey GJ, Neu HC: Infective endocarditis—An evolving disease. Medicine (Baltimore) 57:105-127, 1978

42. Katz D, Cooper JA, Frieden J: Bacterial endocarditis presenting as complete heart block with paradoxical (left-to-right) pulmonary emboli. Am Heart J 85:108-112 1973

43. Banks T, Fletcher A, Ali N: Infective endocarditis in heroin addicts. Am J Med 55:444-451, 1973

44. Ramset RG, Gunnar RM, Tobin JR: Endocarditis in the drug addict. Am J Cardiol 25:608-618, 1970

45. Openshaw H: Neurological complications of endocarditis in persons taking drugs intravenously. West J Med 124:276-281, 1976

46. Jones HR: Neurologic manifestations of bacterial endocarditis. Ann Intern Med 71:21-27, 1969

47. Greenlee JE, Mandell GL: Neurological manifestations of infective endocarditis—A review. Stroke 4:958-963, 1973

48. Ziment I: Nervous system complications in bacterial endocarditis. Am J Med 47:593-607, 1969

49. Cates JE, Christie RV: Subacute bacterial endocarditis. Q J Med 20:93-130, 1951

50. Alexander R, Holloway A, Honsinger RW: Surgical debridement for resistant bacterial endocarditis. JAMA 210:1757-1759, 1969

51. Wilson R, Hamburger M: Fifteen years' experience with staphylococcal septicemia in a large city hospital—Analysis of 55 cases in the Cincinnati General Hospital 1940-1954. Am J Med 22:437-457, 1957

52. Katz RI, Goldberg HI, Selzer ME: Mycotic aneurysm—Case report with novel sequential angiographic findings. Arch Intern Med 134:939-942, 1974

53. Gilroy J, Andaya L, Thomas VJ: Intracranial mycotic aneurysms and subacute bacterial endocaritis in heroin addiction. Neurology (Minneapolis) 23:1193-1198, 1973

54. Ishikawa M, Waga S, Moritake K, et al: Cerebral bacterial aneurysms—Report of three cases. Surg Neurol 2:257-261 1974

55. Hourihane JB: Ruptured mycotic intracranial aneurysms—A report of three cases. Vasc Surg 4:21-29, 1970

56. Bingham W: Treatment of mycotic intracranial aneurysms. J Neurosurg 46:428-437, 1977

57. Moskowitz MA, Rosenbaum AE, Tyler HR: Angiographically monitored resolution of cerebral mycotic aneurysms. Neurology 24:1103-1108, 1974

58. Suwanwela C, Suwanwela N, Charuchinda S, et al: Intracranial mycotic aneurysms of extracranial origin. J Neurosurg 36:552-559, 1972

59. Ziment I: Angiography in the management of intracranial mycotic aneurysms. Arch Intern Med 122:349-362, 1968

60. Cantu RC, LeMay M, Wilkinson HA: The imsportance of repeated angiography in the treatment of mycotic-embolic intracranial aneurysms. J Neurosurg 25:189-193, 1966

61. Roth M: Ueber Netzhaut Affectionen bei Wundfiebern. Deutsch Ztschr Chir 471-484, 1872

62. Litten M: Ueber akute maligne Endocarditis und die dabei vorkommenden Retinal-veranderungen. Charite Ann 3:137-172, 1876

63. Kennedy JE, Wise GN: Clinicopathological correlation of retinal lesions—Subacute bacterial endocarditis. Arch Ophthalmol 74:658-662, 1965

64. Repine JE, Clawson CL, Burchell HB, et al: Reversible neutrophil defect in patients with bacterial endocarditis. J Lab Clin Med 88:780-787, 1976

65. Case 30-1974, Case records of Massachusetts General Hospital: Fever of unknown origin with severe thrombocytopenia. N Engl J Med 291:242-249, 1974

66. Bayer AS, Theofilopolous AN, Eisenberg R, et al: Thrombotic thrombocytopenic purpura-like syndrome associated with infective endocarditis. JAMA 238:408-410, 1977

67. Parsons WB, Cooper T, Scheifley CH: Anemia in bacterial endocarditis. JAMA 153:14-16 1953

68. Joyce RA, Sande MA: Mechanism of anemia in experimental bacterial endocarditis. Scand J Haematol 15:306-311, 1975

69. Corrigan JJ, Jordan CM: Heparin therapy in septicemia with disseminated intravascular coagulation. N Engl J Med 283: 778-782, 1970

70. Colman RW, Robboy SJ, Minna JD: Disseminated intravascular coagulation—An approach. Am J Med 52:679-689, 1972

71. Churchill MA, Gerachi JE, Hunder GG: Musculoskeletal manifestations of bacterial endocarditis. Ann Intern Med 84: 754-759, 1977

72. Tompsett R: Bacterial endocarditis—Changes in the clinical spectrum. Arch Intern Med 119:329-332, 1967

73. Myers AR, Schumacher HR: Arthritis of subacute bacterial endocarditis (abstract). Arthritis Rheum 19:813-814, 1976

74. Bayer AS, Brenner RJ, Galpin JE, et al: Severe disabling polyarthritis associated with bacterial endocarditis. West J Med 123:404-407 1975

75. Holler JW, Pecora JS: Backache in bacterial endocarditis. NY State J Med 70:1903-1905, 1970

76. Messner RD, Williams RC, Keslin MH: Glomerulonephritis with subacute bacterial endocarditis—Immunofluorescent studies. Arch Intern Med 132:578-581, 1973

77. Levy RL, Hong R: The immune nature of subacute bacterial endocarditis nephritis. Am J Med 54:645-652, 1973

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Severe Neutropenia in Infectious Mononucleosis

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Mild neutropenia is a well-known concomitant of infectious mononucleosis caused by the Epstein-Barr virus (EBV) occurring in the first weeks of illness. However, severe neutropenia (less than 200 polymorphonuclear leukocytes per μl) is not generally regarded as a complication of infectious mononucleosis. Three patients were seen with severe neutropenia and EBV infection, and an additional eight cases were found in the literature. In two of the latter cases the neutropenia was fatal.

In the 11 cases the severe neutropenia began 14 to 40 days after illness and usually lasted for three to seven days. At the time of severe neutropenia, studies of marrow specimens showed increased proportions of promyelocytes and myelocytes. Our data suggest that EBV infection is the proximate cause of the severe neutropenia in some patients with infectious mononucleosis and that in such cases close observation and early treatment of suspected superinfections is necessary.

INFECTIOUS MONONUCLEOSIS is a common, self-limited illness characterized by fever, pharyngitis, lymphadenopathy, hepatosplenomegaly, atypical lymphocytosis and a positive heterophil agglutinin test.[1-4] Rises in specific antibody titers to the causative agent, the Epstein-Barr virus (EBV) have recently been used to confirm questionable cases.[5,6]

Mild granulocytopenia (1,000 to 1,800 polymorphonuclear cells per μl) early in the course of infectious mononucleosis is well recognized,[7] occurring in as many as 40 percent of cases. The detailed studies by Carter[8] and Cantow and Kostinas[9] documented a reproducible fall in total circulating granulocyte counts during the first and second weeks of illness as the atypical lymphocyte counts were rising. Although severe neutropenia (less than 200 per μl) has been seen in several patients with infectious mononucleosis, this complication is not widely recognized.[1,2,10]

We recently saw three patients with infectious mononucleosis and severe neutropenia. We present the clinical and laboratory findings together with a review of those cases in the literature for which there was complete hematologic and serologic documentation of both infectious mononucleosis and severe neutropenia. These cases show a reproducible pattern of clinical and laboratory

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ABBREVIATIONS USED IN TEXT

anti-EBNA = anti-Epstein-Barr nuclear antigen
anti-VCA = antiviral capsid antigen
CMV = cytomegalovirus
EBV = Epstein-Barr virus
SGOT = serum glutamic oxaloacetic transaminase

observations strongly suggesting EBV as the agent causing severe neutropenia.

Reports of Cases

CASE 1. A 16-year-old girl was first seen on December 1, 1976, for fever, sore throat and malaise. She was taking meprobamate, 400 mg per day, for dysmenorrhea. She was treated with erythromycin for one week but fever, pharyngitis and cervical adenopathy continued, and hepatosplenomegaly subsequently developed. At that time laboratory data included the following values: hematocrit, 36 percent; leukocyte count, 7,400 per cu mm, with 1,700 polymorphonuclear cells per cu mm, 1,850 mature lymphocytes per cu mm, 3,700 atypical lymphocytes per cu mm and 150 monocytes per cu mm; normal platelets; erythrocyte sedimentation rate, 26 mm per hour; bilirubin, 0.7 mg per dl; alkaline phosphatase, 330 IU per liter; lactic dehydrogenase, 405 units per ml; serum glutamic oxaloacetic transaminase (SGOT), 235 units per ml, and a positive heterophil test.

An examination on December 22 showed no hepatosplenomegaly and the liver enzyme values had returned toward normal, despite the patient's continuing malaise. On December 29, a physical examination gave normal findings, but laboratory studies showed a leukocyte count of 2,200 per cu mm, with 154 polymorphonuclear cells per cu mm, 1,100 mature lymphocytes per cu mm, 880 atypical lymphocytes per cu mm and 66 monocytes per cu mm. The hematocrit was 39 percent; reticulocyte count, 0.6 percent; erythrocyte sedimentation rate, 7 mm per hour, and platelets were normal. A bone marrow aspirate showed normal cellularity with an increased myeloid:erythroid ratio of 4:1. There was an increase in promyelocytes and myelocytes with very few band cells or segmented neutrophils. One week later, the leukocyte count was 3,500 per cu mm, with 900 polymorphonuclear cells per cu mm, 180 band cells per cu mm, 2,170 lymphocytes per cu mm including atypical forms, and 280 monocytes per cu mm. By January 11, 1977, the leukocyte count and cell count differential were normal but the heterophil test remained positive. In April 1977, pharyngitis consistent with a mild viral infection developed, and elevation of the heterophil titer was noted (positive at 1:28). Serologic tests for EBV infection* showed an antiviral capsid antigen titer (anti-VCA, IgG) of 1:2,560 and an anti-Epstein-Barr nuclear antigen titer (anti-EBNA) of 1:40, findings consistent with a previous EBV infection.

Comment. This patient had a typical case of clinical infectious mononucleosis in December 1976. Blood smear and serology confirmed the diagnosis at that time; unfortunately, only one serum specimen was available for detailed serologic studies and was helpful only in showing previous infection by the Epstein-Barr virus.

CASE 2. Two weeks before admission to hospital, a 36-year-old woman noted an aching pain in the left posterior part of the neck associated with fatigue and malaise. Six days before admission she began having shaking chills, fevers and sweats; four days later she felt lumps on her neck.

At admission on September 2, 1977, her only complaint was of a mild epigastric pain. At home she had regularly supervised dialysis therapy for her husband, who had chronic renal failure. He was HAA (hepatitis-associated antigen) negative and had not been admitted to hospital in the previous two years. She had taken no medications except acetylsalicylic acid rarely for headaches. She gave no family history of blood diseases. In her work she was exposed to fertilizer dusts and insecticides. On examination the patient was afebrile and had shotty anterior and posterior cervical adenopathy, two small high occipital lymph nodes and a palpable spleen tip. The leukocyte count was 16,800 per cu mm with 8,400 atypical lymphocytes, 8,200 normal lymphocytes and 200 monocytes per cu mm, and no neutrophils. Hematocrit was 39 percent; reticulocyte count, 1.3 percent; platelets normal on smear; erythrocyte sedimentation rate, 33 mm per hour; SGOT, 125 units per ml, and a Monospot test was equivocally positive. Repeat Monospot test was negative and tests for toxoplasma, cytomegalovirus (CMV) herpes simplex and rubella infections were also negative. Serology for EBV infection showed anti-VCA (IgG) titer of 1:160,

*Serologic tests for Epstein-Barr virus in cases 1, 2 and 3 were done by Dr. Werner Henle, Director, Division of Virology, The Joseph Stokes, Jr. Research Institute, The Children's Hospital of Philadelphia, Philadelphia.

anti-VCA (IgM) titer of 1:640 and an anti-EBNA titer of 1:5 on September 7. Repeat titers were 1:160, 1:320 and 1:10, respectively, on September 15 and 1:80, less than 1:10 and 1:20, respectively, on October 12.

Blood smears showed rare neutrophils over the next three days. A marrow study on September 6 showed myeloid hyperplasia with normal maturation to band forms. At that time a few segmented neutrophils were identified on a blood smear. On September 15 the leukocyte count was 7,000 per cu mm, with 460 polymorphonuclear cells per cu mm, and the patient was clinically improved. Weekly blood counts showed continuing resolution of the granulocytopenia, and the patient reported that the symptoms were completely gone by October 12.

Comment. This patient had a clinically atypical case of infectious mononucleosis. Our initial hypothesis that her illness might be due to toxoplasma, CMV, herpes simplex, or rubella infection could not be confirmed serologically. The diagnosis of EBV infection is based on characteristic serologic changes of a recent primary EBV infection. The falling titer of IgM antibody to viral capsid antigen (anti-VCA, IgM) and rising titer of antibody to Epstein-Barr nuclear antigen (anti-EBNA) are sequential changes diagnostic of recent EBV infection.[5,6]

CASE 3. In a 32-year-old man sore throat, malaise, myalgias and headaches developed in December 1974. The symptoms persisted until March 1975 when he was first seen by a physician, who noted tender cercival adenopathy and an injected pharynx but no hepatosplenomegaly. The leukocyte count was 6,600 per cu mm, with 3,300 neutrophils, 2,000 atypical lymphocytes and 660 monocytes per cu mm. A Monospot test was positive.

The patient's symptoms persisted until April 17 when he noted increased sore throat and headache without fever or chills. He said he had taken no drugs except acetylsalicylic acid and chlorpheniramine, and he did not recall exposure to other known toxins. On physical examination the man appeared acutely ill. Temperature was 39.4°C (103°F), there was severe exudative pharyngitis, and tender cervical and submandibular adenopathy, without hepatosplenomegaly. Laboratory studies showed a hematocrit of 35.3 percent; hemoglobin, 12.0 grams per dl; reticulocyte count, 0.2 percent, and platelet count, 109,000 per cu mm. The leukocyte count was 1,000 per cu mm, with 940 lymphocytes which were predominantly atypical, 40 monocytes and 20 basophils per cu mm. A marrow aspirate showed a substantial decrease in the number of myeloid elements with only rare myeloblasts and promyelocytes and no segmented granulocytic elements.

Other laboratory tests showed a bilirubin value of 1.3 mg per dl with normal SGOT, lactic dehydrogenase (LDH) and alkaline phosphatase levels. Repeat Monospot test was positive again and serology for CMV was negative. Serology for EBV infection gave an anti-VCA (IgG) titer of 1:40 and an anti-EBNA titer of less than 1:2 on April 19. On May 1, repeat values were 1:160 for anti-VCA (IgG) and 1:10 for anti-EBNA.

After collecting specimens for culture (all cultures subsequently were negative), administration of penicillin and gentamicin was begun. Fever and agranulocytosis persisted through hospital day 4 with the total leukocyte count remaining less than 2,000 per cu mm and no polymorphonuclear cells seen on smear. On day 5 the total leukocyte count rose to 2,100 per cu mm and 7 percent polymorphonuclear cells were noted. At this time the patient's fever abated and antibiotic therapy was discontinued. By day 8 the total leukocyte count had risen to 5,300 per cu mm with 1,800 neutrophils per cu mm; hematocrit, 38 percent, and platelets, 421,000 per cu mm. The patient was discharged. Over the next three months malaise and fatigue persisted but adenopathy gradually resolved. Occasional atypical lymphocytes persisted on peripheral smear for up to four months after discharge.

Comment. This patient's illness was also unusual for infectious mononucleosis. His prolonged prodrome was not well documented and may have been a separate illness. At the time of the first evaluation in March 1975, the patient appeared to have infectious mononucleosis. The subsequent detailed serologic changes are consistent with a primary EBV infection.

Discussion

The occurrence of mild decreases in granulocyte counts early in infectious mononucleosis was first documented in the classic monograph by Downey and McKinlay.[7] Later studies supported the occurrence of this phenomenon, showing that a fall in total circulating granulocyte numbers regularly occurred in up to 40 percent of cases

during the first and second weeks of illness.[8,9] Although several case reports have suggested that severe, life-threatening granulocytopenia may occur with infectious mononucleosis,[11,14,18,19,21-27] concurrent drug or toxin exposures and incomplete reporting of case data make interpretation of the relationship difficult.

The diagnosis of infectious mononucleosis is based on the clinical pattern of illness, atypical lymphocytosis in the blood and the presence of heterophil agglutinins in the serum. In a small proportion of patients with clinical features of mononucleosis, heterophil agglutinin tests have been reported as negative. Although a few of these patients with heterophil-negative mononucleosis syndromes may actually have heterophil agglutinins demonstrable with horse erythrocyte reagents rather than with sheep erythrocyte materials, in some more sophisticated serologic testing is required. Specific tests for antibody to EBV-induced antigenic determinants can differentiate mononucleosis syndromes due to cytomegalovirus from those due to the Epstein-Barr virus.[6] Although in our patients there were variable clinical manifestations of the mononucleosis syndrome, in all three large numbers of circulating atypical lymphocytes were seen on blood smear. In two of our patients there were heterophil agglutinins with appropriate differential absorption patterns (cases 1 and 3) while a study in the third was negative. In this latter patient the EBV-specific serologic tests showed serial changes similar to those reported previously in patients with heterophil-negative infectious mononucleosis due to the Epstein-Barr virus.[6]

The three cases we have presented showed severe neutropenia in association with serologically well-documented infectious mononucleosis syndromes due to the Epstein-Barr virus. The pattern of onset in relation to the viral infection, duration of severe neutropenia and recovery of blood counts suggested the possibility that the EBV caused the decreased counts. Other causes of severe neutropenia such as drug or toxin exposure appear unlikely in our cases because each patient either inadvertently continued to take the potential agent (meprobamate, case 1) or was reexposed by returning to work (cases 2 and 3) or taking the nonprescription drug again (acetylsalicylic acid and chlorpheniramine, case 3) without evident harm.

The cases of severe neutropenia (less than 200 per μl) from the literature show that the temporal and morphologic findings we have noted are not peculiar to our patients (see Table 1). Six of the eight case reports from the literature that had adequate data for review showed almost identical marrow histology with a prominence of promyelocytes (with or without myelocytes) and a decrease in or lack of more mature neutrophils; the remaining two case reports showed myeloid hyperplasia. The time course of the neutropenia was also similar among the cases, confirming the impression that this extreme neutropenia is a self-limited process and suggesting a causal relationship. In each case acceptable serologic data are provided to support the clinical diagnosis of infectious mononucleosis. Several possible cases were omitted for lack of sufficiently detailed reports.[10(cases 1 and 2),11(case 1),12-20]

Detailed review of the cases of severe neutropenia in Table 1 shows several common features. First, the age and sex distributions are usual for infectious mononucleosis except for case 10. Second, the onset of severe neutropenia occurs from 14 to 40 days after symptoms begin, generally later than the previously noted mild granulocytopenia. Third, the time course of the neutropenia is extraordinarily predictable: in eight of the nine patients who recovered, the granulocyte count exceeded 500 per μl within 3 to 7 days, and in the two patients who died, the supervening fatal bacterial infections (Staphylococcus aureus in both cases) occurred very soon after discovery of neutropenia, at 1½ and 3 days. Fourth, in three of these 11 cases (cases 2, 9 and 10) myeloid hyperplasia was noted, while in the remaining eight, promyelocytes and myelocytes were present or increased and more mature neutrophilic cells were depleted.

In our patients bone marrow studies showed intact populations of promyelocytes and myelocytes with a relative or absolute decrease in mature neutrophils in two patients and myeloid hyperplasia in the third; these findings might be seen in several different situations. The term *maturation arrest* was used for these marrow findings in cases 4, 5 and 8 from our literature review. However, the fact that the blood counts generally returned to normal within five to seven days suggests that the marrow findings represent a proliferative response to an earlier marrow cell injury. The repeat marrow aspirates in case 11 support this view. Although we have no evidence at present as to the pathophysiology of the severe neutropenia in these persons our review of the

TABLE 1.—*Clinical and Laboratory Data in 11 Patients With Infectious Mononucleosis and Severe Neutropenia*

Case	Age (Years)	Sex	Time* (Days)	Lowest Leukocyte Count (cells/μl)	Lowest PMN Count (cells/μl)	Duration of Neutropenia (Days)	Hematocrit/Platelet Count (per cu mm)	Bone Marrow Findings	Serology	Drug Exposure	Therapy and Comments
Present Series											
1	16	F	34	2,200	154	7	39 percent/normal	Pronounced increase of promyelocytes and myelocytes	HA+	Meprobamate	Lived; no alteration of meprobamate dosage, no other drug exposure
2	36	F	16	7,000	0	11	40 percent/238,000	Myeloid hyperplasia, normal maturation	See text	Insecticide and fertilizer dusts	Lived; no corticosteroids, no antibiotics, no other drug exposure
3	32	M	40	1,000	0	5	35 percent/109.000	Absence of myeloid elements beyond the promyelocytes; relatively normal erythroid and megakaryocyte series	Monospot+	Acetylsalicylic acid, chlorpheniramine, paint fumes	Lived; antibiotics; leukoagglutinins negative; persistent symptoms and atypical lymphocytes
Literature Series											
4	19	M	32	3,800	38	3	34 percent/170,000	Normal erythroid and megakaryocytic lines; block of maturation beyond promyelocyte	Paul Bunnell +1:640	Pyramidon (aminopyrine), Salgydal	Lived; treated with hydrocortisone for Guillain-Barré syndrome before neutropenia; no leukocyte antibodies found[28]
5	19	F	26	2,000	0	7	34 percent/103,000	Complete arrest of promyelocytes with normal erythroid and megakaryocyte series	HA+1:128	Before onset of symptoms, none; at onset of symptoms: penicillin, tetracyline; phenacetin, codeine, acetylsalicylic acid	Lived; treated with prednisone after agranulocytosis diagnosed; leukoagglutinins negative; sister died of leukemia at age 5 years[23]
6	19	M	20	3,400	0	5	NR	Absence of mature polymorphonuclear cells; increased promyelocytes and myelocytes; normocellular	Monospot+	At onset of symptoms: acetylsalicylic acid, penicillin	Lived; treated with prednisone and nonabsorbable oral antibotics; leukoagglutinins negative; 18 percent atypical lymphocytes after 83 days[24]
7	29	M	14	1,800	0	3	44 percent/204,000	Normocellular, no cells beyond promyelocyte	HA+1:896	NR	Lived; treated with oxacillin, gentamicin and prednisone after neutropenia diagnosed; leukoagglutinins negative; 10 percent atypical lymphocytes after 60 days[11]
8	35	F	40	2,200	0	3	40 percent/133,000	Late maturation arrest of myeloid series	HA+ >1:4,000	Mefenamic acid; barbiturates	Lived; treated with penicillin and pethidine after neutropenia diagnosed; persistent headache and abnormal cerebrospinal fluid for months after; jaundice[25]
9	24	M	15	6,500	0	1½	35 percent/ 78,000	Myeloid hyperplasia, maturation normal	Ox cell hemolysin titer+ 1:960	At onset of symptoms: penicillin	Died of Staphylococcus aureus pneumonia with acute respiratory distress syndrome; had been treated with penicillin, methicillin; no corticosteroids given[27]
10	2	M	20	2,700	162	3	37 percent/ 96,000‡	Myeloid hyperplasia, adequate megakaryocytes	HA+1:224 Monospot−	At onset of symptoms: ampicillin	Died; S. aureus and Hemophilus influenzae in blood, pneumonia and Reye syndrome; had been treated with ampicillin for three doses, then cephalothin and gentamicin for three days; no corticosteroids given; two uncles died of leukemia in childhood[26]
11	19	M	23	1,500	0	6	NR†/NR	Myeloid hypoplasia, with only promyelocytes seen initially; four days later, marrow myeloid hyperplasia	HA+1:896	At onset of symptoms: penicillin and sulfadiazine	Lived; treated with sulfonamides four months before illness; penicillin during neutropenia; no corticosteroids given[22]

HA = heterophil agglutinin NR = not recorded PMN = polymorphonuclear cell + = reported as positive

data shows that severe neutropenia can be an important complication of infectious mononucleosis. Until the pathogenesis of this complication is clearly understood, and early or preventive treatment shown to be useful, we recommend close observation of these patients and early treatment of suspected superinfections.

REFERENCES

1. Wintrobe MM, Lee GR, Boggs DR, et al: Clinical Hematology, 7th Ed. Philadelphia, Lea and Febiger, 1974, pp 1356-1376
2. Williams WJ, Beutler E, Erslev AJ, et al: Hematology, 2nd Ed. New York, McGaw-Hill Book Company, 1977, pp 956-968
3. Carter RL, Penman HG: Infectious Mononucleosis. Oxford, Blackwell Publications, 1969
4. Lee CL, Davidsohn I, Panczyszyn O: Horse agglutinins in infectious mononucleosis—II. The Spot test. Am J Clin Pathol 49:12-18, 1968
5. Horwitz CA, Henle W, Henle G, et al: Clinical evaluation of patients with infectious mononucleosis and development of antibodies to the R component of the Epstein-Barr virus-induced early antigen complex. Am J Med 58:330-338, 1975
6. Horwitz CA, Henle W, Henle G, et al: Heterophil-negative infectious mononucleosis and mononucleosis-like illnesses. Am J Med 63:947-957, 1977
7. Downey H, McKinlay CA: Acute lymphadenosis compared with acute lymphatic leukemia. Arch Intern Med 32:82-112, 1923
8. Carter RL: Granulocyte changes in infectious mononucleosis. J Clin Pathol 19:279-283, 1966
9. Cantow EF, Kostinas JE: Studies on infectious mononucleosis—IV. Changes in the granulocytic series. Am J Clin Pathol 46:43-47, 1966
10. Penman HG: Extreme neutropenia in glandular fever. J Clin Pathol 21:48-49, 1968
11. Kosiner B, Hadler N, Parrillo J, et al: Agranulocytosis following infectious mononucleosis. JAMA 225:1235-1236, 1973
12. Claveaux E, Uanzani R, Salveraglio F: Mononucleosis infecciosa seguida de agranulocitosis aguda con gram monocitosis sanguinea. Arch Urg Med 22:136-151, 1943
13. Stevens JE, Bayrd ED, Heck FJ: Infectious mononucleosis—A study of 210 sporadic cases. Am J Med 11:202-208, 1951
14. Fisher BD: Neutropenia in infectious mononucleosis. N Engl J Med 288:633, 1973
15. Purtilo DT, Yang JPS, Cassell CK, et al: X-linked recessive progressive combined variable immunodeficiency (Duncan's disease). Lancet 1:935-941, 1975
16. Purtilo DT: Pathogenesis and phenotypes for an X-linked recessive lymphoproliferative syndrome. Lancet 2:882-885, 1976
17. Purtilo DT: Opportunistic non-Hodgkin's lymphoma in X-linked immunodeficiency and lymphoproliferative syndromes. Sem Oncol 4:335-343, 1977
18. Purtilo DT, DeFlorio D Jr, Hutt LM, et al: Variable phenotypic expression of an X-linked recessive lymphoproliferative syndrome. N Engl J Med 297:1077-1081, 1977
19. Bar RS, DeLor CJ, Clausen KP, et al: Fatal infectious mononucleosis in a family. N Engl J Med 290:363-367, 1974
20. Provisor AJ, Iacuone JJ, Chilcote RR, et al: Acquired agammaglobulinemia after a life-threatening illness with clinical and laboratory features of infectious mononucleosis in three related male children. N Engl J Med 293:62-65, 1975
21. Penman HG: Fatal infectious mononucleosis: A critical review. J Clin Pathol 23:765-771, 1970
22. Stroebel CF, Hallberg OE, Stevens JE Jr: Infectious mononucleosis and agranulocytosis—Report of a case. Ann Otol Rhinol Laryngol 57:1102-1112, 1948
23. Wulff HR: Acute agranulocytosis following infectious mononucleosis.—Report of a case. Scand J Haem 2:179-182, 1965
24. Habib MA, Bakka JC, Burmingham RA: Profound granulocytopenia associated with infectious mononucleosis. Am J Med Sci 265:339-346, 1973
25. Munro AHG, Degnen F, Munro JF: Infectious mononucleosis and agranulocytosis. Scand J Infect Dis 3:249-250, 1971
26. Dorman JM, Glick TH, Shannon DC, et al: Complications of infectious mononucleosis. Am J Dis Child 128:239-243, 1974
27. Neel EU: Infectious mononucleosis—Death due to agranulocytosis and pneumonia. JAMA 236:1493-1494, 1976
28. Leng-Levy J, Castaing R, Aubertin J: Mononucleose infectieuse et syndrome de Guillaine-Barré. Bordeux Med 3:2065-2070, 1970

Use of Metronidazole (Flagyl) Contraindicated in First Trimester of Pregnancy

WHAT IS THE TREATMENT of trichomoniasis in pregnancy? Animal data suggest that metronidazole (Flagyl) is contraindicated during the first trimester and is probably safe during the second and third trimesters. I would try to avoid it, if possible, all the time during pregnancy. If a woman comes in during the first trimester with trichomoniasis, I will treat her with local therapy. I prefer to use vinegar douching—two tablespoons of vinegar in a quart of warm water—and instruct her how to douche in pregnancy; you have to do it very gently. The reason I prefer that is that it restores the normal pH of the vagina; it is essentially antagonistic to the trichomonas; and it does not distort normal vaginal flora.

—MICHAEL F. REIN, MD, *Charlottesville, Virginia*

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Congenital Dislocation of the Hip

Prognostic Implications of Early Diagnosis

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A retrospective analysis of 62 patients with 78 congenital dislocations of the hip (CDH) referred to Children's Hospital at Stanford was done to ascertain whether CDH was being diagnosed as early as had been thought possible and whether various treatments were effective. In this series there were a substantial number of cases of CDH that were not diagnosed within the first 48 hours of life. At Children's Hospital the Pavlik harness was the most effective form of treatment of congenital dislocations of the hip in the perinatal period.

MANY PHYSICIANS now believe that with the use of a few simple clinical tests and the subsequent application of a few simple devices, congenital dislocation of the hip (CDH) can be readily diagnosed and treated. Reports from Malmö[1,2] and Manchester[3] have set high standards for both sensitive screening for CDH and effective therapy. However, in a recent assessment by Jones and co-workers[4] of examinations of the hips in newborn infants, it was concluded that 50 percent of the cases of CDH were missed despite examinations during the first 48 hours of life. Furthermore, different authors have reported difficulties with treatment despite early diagnosis.[5-8]

The questions raised in this study are (1) Is CDH being diagnosed as early as has been thought possible—that is, within the first 48 hours after birth? (2) If CDH is diagnosed within 48 hours, are a variety of splinting techniques all equally effective, or is there one device that is most effective?

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Children's Hospital at Stanford is a referral center for pediatrics in the San Francisco Bay area. Between 1972 and 1977, there were 62 patients with 78 congenital dislocations of the hip seen in consultation. This paper presents a retrospective analysis of these cases and focuses on the time of diagnosis and the efficacy of management.

Case Material

All of the 62 cases of CDH referred to the hospital between 1972 and 1977 were reviewed with respect to the age of the patients at the time of diagnosis and at the time of referral, the therapy undertaken and results of therapy. Diagnosis was based on clinical instability of the hip as described by Le Damany,[9] Ortolani[10] and Von Rosen,[11] and roentgenographic confirmation according to Hilgenreiner[12] or Von Rosen[11] or both. Of the 62 patients, 51 were girls and 11 were boys. The left hip was dislocated in 29 patients, the right hip in 17 and both hips in 16.

Two groups were distinguished: Group 1 consisted of 64 hips in infants who were referred after the diagnosis was made and treatment had

TABLE 1.—*Forms of Primary Therapy in 62 Patients (78 Hips)*

Number of Patients	*Number of Hips*	*Therapy*
9	11	triple diapers
15	19	abduction devices
13	15	Pavlik harness
17	22	closed reduction
8	11	open reduction

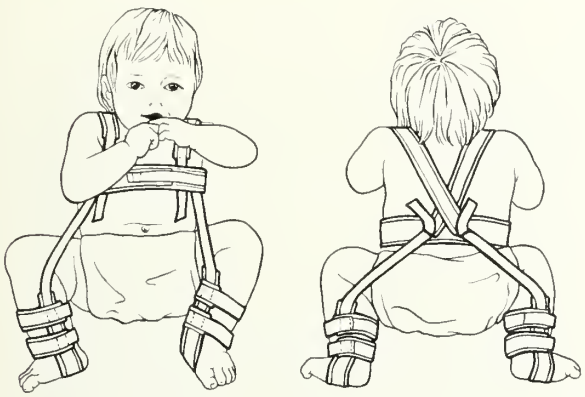

Figure 1.—The Pavlik harness, when well-fitted, keeps both hips flexed in "human position" and allows a good range of motion in abduction and adduction.

been instituted elsewhere. The reason for referral in 44 cases (57 hips) was failure of initial treatment. In five patients (seven hips) referral was made for a second opinion concerning the type of treatment. Group 2 consisted of 13 patients with 14 dislocated hips referred before treatment. The condition was diagnosed in four of these after one year of age, and in two between four months and one year of age. Only three of these dislocations were discovered within the first 48 hours of life.

Methods

Forms of treatment were divided into four general classifications: (1) triple diapers, (2) abduction devices (Barlow, Von Rosen and Craig splints, and the Frejka pillow), (3) the Pavlik harness and (4) traction and closed reduction. Open reduction was done in some cases but results of this treatment are beyond the scope of this paper and, therefore, not reported (Table 1). In this institution the Pavlik harness[13] (Figure 1) and open reduction were the principal methods of treatment. Follow-up included both clinical and roentgenographic examinations. The mean duration of follow-up has been 3 years and 9 months with a range of 5 months to 14 years.

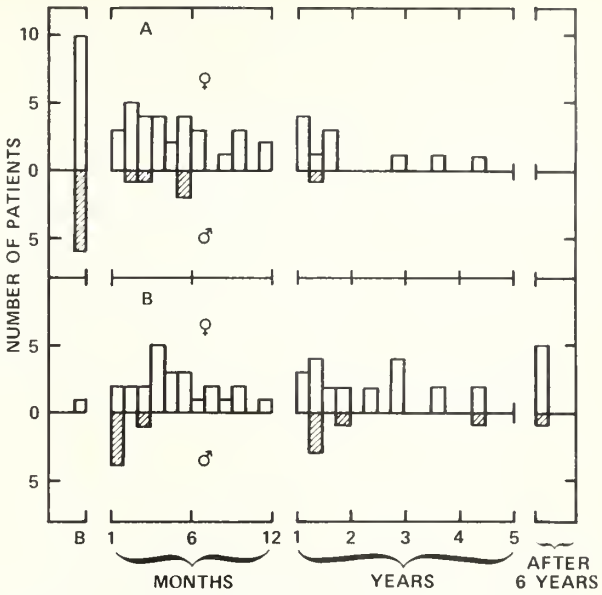

Figure 2.—Patients in the study (males, crosshatched bars). **A,** Age at diagnosis. **B,** Age at referral.

Results

Age at Initial Diagnosis

In 16 patients congenital dislocation of the hip was diagnosed at birth (less than 48 hours after birth), in 14 it was diagnosed between 48 hours and four months, in 20 between 4 and 12 months and in 12 more than 12 months after birth. Only one patient was referred at the time of birth while 33 were referred after the age of one year. Six were not referred until the age of six years. (See Figure 2.)

Types of Initial Treatment

Tables 2 through 5 show the effectiveness of treatment. Success was defined as that which required no further therapy. Failure was defined using three criteria: (1) complete failure of relocation or redislocation, (2) partial failure due to residual acetabular dysplasia and (3) partial failure due to aseptic necrosis of the femoral capital epiphysis.

Triple Diapers

In nine patients, 11 dislocatable hips were treated with triple diapers (Table 2). In ten of these, hips relocation did not occur and four were subsequently treated successfully with a Pavlik harness. Of these four, three had been diagnosed within 48 hours after birth and one had been diagnosed between 48 hours and four months after birth. In the other six hips treated unsuc-

TABLE 2.—*11 Hips Treated With Triple Diapers*

	Success	*Failure*
Within the first 48 hours ...	..	5
Third day to fourth month ..	..	5
After the fourth month	1	..

TABLE 3.—*26 Hips Treated With an Abduction Device, 19 as a Primary Treatment*

	Success	*Dysplasia*	*Redis-location*	*Aseptic Necrosis*
Primary treatment				
Within the first 48 hours	4	1(?)	3	2
Third day to fourth month	1	..	3	..
After the fourth month	3	3	1	..
Secondary treatment .	3	..	4	..

TABLE 4.—*29 Hips Treated With a Pavlik Harness, 15 as a Primary Treatment*

	Success	*Dysplasia*	*Redis-location*	*Aseptic Necrosis*
Primary treatment				
Within the first 48 hours	3	..	..	..
Third day to fourth month	7	..	..	..
After the fourth month	3	2	..	..
Secondary treatment	8	1	3	2

cessfully with triple diapers, closed or open reduction was necessary for relocation. The only case with a successful outcome in this group treated with triple diapers was one in which initial treatment with diapers was delayed until four months after birth and no further treatment was required.

Abduction Devices

Abduction devices were used as initial treatment of 19 hips in 15 patients (Table 3). The mean duration of follow-up in this group was three years, two months (with a range of six months to eight years). The result was successful in eight hips in seven patients. Three patients were referred for completion of treatment previously instituted. In one patient dysplasia of the acetabulum appeared which resolved with prolonged treatment with an abduction device. In one patient the hip was relocated, but abduction and flexion contracture developed. An arthrogram of the hip was required for evaluation and the contractures were relieved with traction.

Among 11 hips in which treatment failed (eight patients), seven were failures of relocation and three showed persistent acetabular dysplasia at the time of follow-up (34 months). In the third patient with acetabular dysplasia in one hip, bilateral aseptic necrosis of the femoral capital

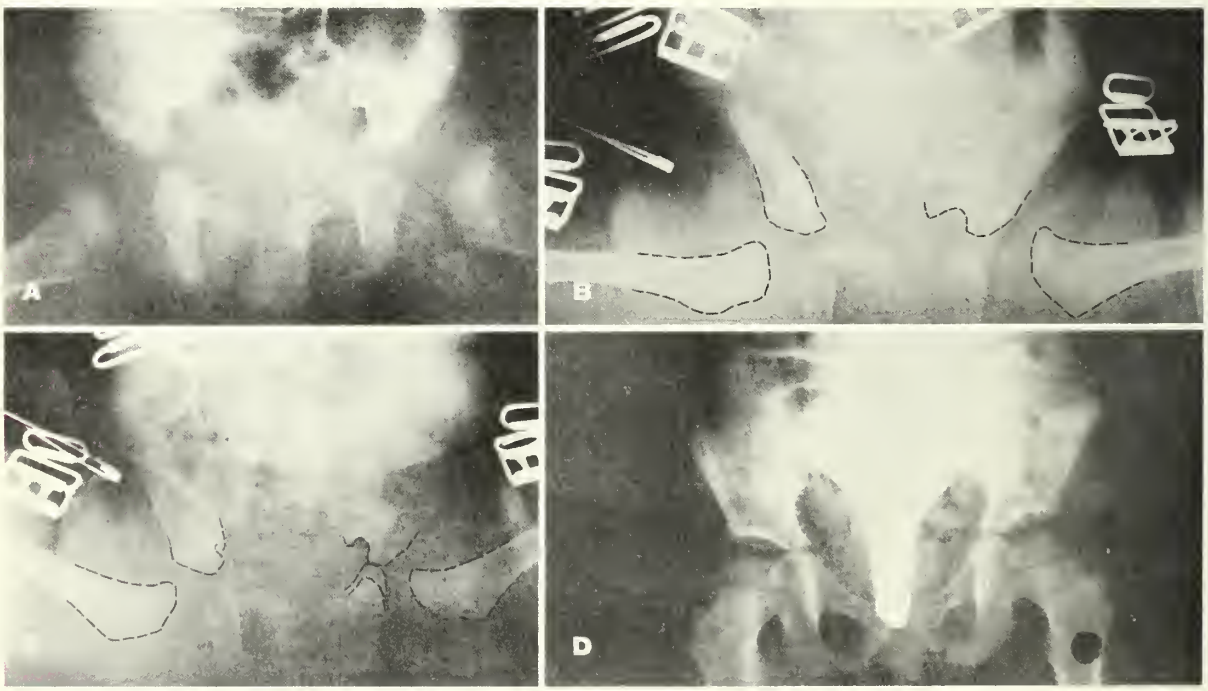

Figure 3.—Congenital dislocation of the left hip diagnosed at birth. **A,** Initial treatment with triple diapers failed to achieve relocation. **B,** Application of Pavlik harness at age two months. **C,** After one month of treatment, relocation is obtained. **D,** Result at two years of age is satisfactory.

epiphysis appeared following treatment with a Barlow splint for a unilateral dislocatable hip.

Pavlik Harness

Primary treatment. A total of 15 hips in 13 patients were treated initially with a Pavlik harness (Table 4). Reduction was accomplished in all 15 and the mean duration of follow-up was 11½ months. However, acetabular dysplasia developed in two of these. One was in a child whose treatment commenced at one year of age, and the other was diagnosed at the age of five months following which the harness was then used for four months. *Secondary treatment.* Fourteen hips in 11 patients were treated with a Pavlik harness after other treatments had failed (Figure 3, Table 4). In two of these, aseptic necrosis of the femoral capital epiphysis developed; however, in these two the initial treatment had been closed reduction. In one case with dislocation of both hips, aseptic necrosis occurred only in the left. In three of the 14 hips, relocation did not occur, and of these two had been treated previously with closed reduction and one had been treated with a Frejka pillow. In two cases with dislocation of both hips, initial treatment resulted in relocation of the right hip but not the left. In one case there was persistent acetabular dysplasia following initial treatment with closed reduction and plaster immobil-

Figure 4.—Diagnosis of congenital dislocation of the left hip delayed to age 17 months. **A,** Roentgenogram at beginning of treatment. Relocation was obtained after ten days of traction. Containment was subsequently attempted with frog-leg spica cast. **B,** Roentgenogram at end of treatment shows that the frog-leg position resulted in inferior and anterior dislocation.

TABLE 5.—*31 Hips Treated With Closed Reduction, 22 as a Primary Treatment*

	Success	*Dysplasia*	*Redis-location*	*Aseptic Necrosis*
Primary treatment				
Within the first 48 hours	1	1	1	..
Third day to fourth month	1	..	..	2
After the fourth month	1	6	7	2
Secondary treatment	1	3	5	..

Figure 5.—Diagnosis of congenital dislocation of the hip delayed to age 4 months. Initial treatment with abduction splint, followed by spica cast after manipulation. Late roentgenogram shows acetabular dysplasia and sequelae of aseptic necrosis.

ization for six weeks; after this, a Pavlik harness was applied for an unknown duration. This patient was seen by us five years after initial treatment when persistent subluxation of the right hip was present.

Closed Reduction

Of 22 hips in 17 patients treated initially with closed reduction, there was redislocation in eight (Figure 4, Table 5). In one bilateral case, treatment of both hips failed. In seven hips acetabular dysplasia developed and in four, aseptic necrosis of the femoral capital epiphysis occurred. (Figure 5). Of the nine cases given secondary treatment with closed reduction, there were no further sequelae in one hip, redislocation occurred in five and acetabular dysplasia eventually developed in three.

Ultimately in the entire group of 78 dislocations of the hip, open reduction was required in 28 hips, either initially or after failure of one or more previous attempts at relocation by other methods.

Discussion

Is progress being made in preventing persistent dislocation of the hip by early diagnosis in newborn infants? Of the 62 patients referred to us with a diagnosis of CDH, the condition was diagnosed in only 25 percent within the first 48 hours after birth, and in almost 20 percent after 12 months. These data must be compared to such studies as those done in Malmö[1] and Edinburgh[5] in which diagnosis was delayed beyond the first two days after birth in only 0.007 and 0.0125 percent of the cases, respectively. In contrast, in the study by Jones and co-workers[4] 50 percent of the cases of dislocatable hips were missed by hospital physicians and 72 percent were missed by family physicians. Furthermore, in a survey done at the Tel Aviv University Medical School,[7] treatment of CDH was begun during the first six months after birth in only 71 percent of the cases.

An explanation for the late diagnosis of CDH in some areas of the country probably rests in part with the relative rarity of the problem coupled with low birth rates. Consequently, physicians have difficulty recognizing a disease with subtle clinical findings unless they have had previous experience with it. However, all patients in our study were born in metropolitan hospitals with high standards of practice and most were examined by pediatricians shortly after birth. Therefore, we still do not know whether there is a type of CDH that is clinically silent at birth and presents later with subluxation and acetabular dysplasia.[14-16] There is at least one case in our group that was probably in this category: a patient was examined by many pediatricians after being admitted to hospital for other neonatal problems, and it was felt that there were no clinical signs of dislocation of the hip. The first *scatto* or *ressaut* sign in which the femoral head glided over the acetabular ridge with a jolt was not found until the patient was five months old.

While the issue of early diagnosis of CDH has not been resolved satisfactorily, it is nonetheless indisputable that every infant should be examined for dislocation of the hip during the first 48 hours after birth by using the testing methods of Ortolani and Barlow. Clicks in the hips do not confirm diagnosis. A definite jolt from the exit and reentry of the femoral head into the acetabular cup, once found by an examining physician, is unforgettable and confirms the diagnosis. Examination of the hip in an infant during each visit to a physician during the first year of life continues to be as important as the first neonatal examination for the most satisfactory outcome.[4,17]

A second major consideration is the effectiveness of treatment once the diagnosis has been made, especially in the newborn group. In this study, all of the dislocations of the hip diagnosed early and treated with triple diapers required secondary forms of treatment. In about 50 percent of the patients whose conditions were diagnosed within 48 hours after birth and treated with abduction splints, secondary forms of treatment were necessary as well. It is not possible to compare results of treatment of cases referred after failure of treatment and those sent before treatment. However, if we look at 12 dislocations of the hip treated by us initially with the Pavlik harness, good results with this device seem obvious even in cases referred after the fourth month (Table 6).

Closed reduction was used only in cases in which diagnosis and treatment had been delayed. In cases treated with closed reduction there were major complications including redislocation, acetabular dysplasia and aseptic necrosis of the femoral head.

It must be recalled that the cases reported here represent a skewed group because almost all of the patients were referred only after there had been uncertainty of the management of the con-

dition. The data suggest that even if CDH is diagnosed early and therapy is begun, there still may be complicated courses.

It is thought that in about 80 percent of dislocations of the hip in infants, reduction occurs spontaneously,[3] in which case a patient may fare well regardless of treatment methods. However, it is impossible to predict the group to which a case belongs. The unsatisfactory outcome in nine cases treated with triple diapers and subsequently referred to us points to this inability.

TABLE 6.—*Results of Primary Treatment of 14 Hips at Children's Hospital at Stanford (open reduction in one hip is not reported)*

	Success		*Failure*	
	Pavlik Harness	*Closed Reduction*	*Pavlik Harness*	*Closed Reduction*
Within the first 48 hours	3	..	..	..
Third day to fourth month	6	..	..	..
After the fourth month	2	..	1	2

TABLE 7.—*The 33 (32) Failures Related to Primary Treatment; in 15 Cases Open Reduction Was Done as Secondary Treatment*

	Within the First 48 Hours	*Third Day to Fourth Month*	*After the Fourth Month*
Dysplasia (12)			
Abduction devices	(1?)	..	3
Pavlik harness	..	..	2
Closed reduction	1	..	6
TOTAL	1	..	11
Redislocation (15)			
Abduction devices	3	3	1
Pavlik harness	..	..	..
Closed reduction	1	..	7
TOTAL	4	3	8
Aseptic necrosis (6)			
Abduction devices	2	..	..
Pavlik harness	..	..	..
Closed reduction	..	2	2
TOTAL	2	2	2

Table 7 shows that the most failures in treatment occurred when diagnosis was made late. Of 32 instances in which initial treatment failed (with 33 complications), diagnosis had been made after the fourth month in 21.

We have concluded that the standards of early diagnosis established by such studies as those in Malmö, have not been realized in our area. While CDH might be diagnosed within the 48 hours after birth, this study of referred cases does not prove that early diagnosis necessarily yields the best results. We can conclude from our experience that the Pavlik harness is both an effective and predictable form of treatment when it is accurately fitted and there is careful follow-up.[13]

REFERENCES

1. Fredensborg N: The results of early treatment of typical congenital dislocation of the hip in Malmö. J Bone Joint Surg 58B:272-278, Aug 1976
2. Von Rosen S: Diagnosis and treatment of congenital dislocation of the hip joint in the newborn. J Bone Joint Surg 44B: 284-291, May 1962
3. Barlow TG: Early diagnosis and treatment of congenital dislocation of the hip. J Bone Joint Surg 44B:292-301, Aug 1977
4. Jones D, Boreham W: An assessment of the value of examination of the hip in the newborn. J Bone Joint Surg 59B:318-322, Aug 1977
5. Mitchell GP: Problems in the early diagnosis and management of congenital dislocation of the hip. J Bone Joint Surg 54B:4-12, Feb 1972
6. Walker G: Problems in the early recognition of congenital hip dislocation. Br Med J 3:147-148, Jul 1971
7. Weissman SL, Salama R: Treatment of congenital dislocation of the hip in the newborn infant. J Bone Joint Surg 48A: 1319-1327, Oct 1966
8. Williamson J: Difficulties of early diagnosis and treatment of congenital dislocation of the hip in Northern Ireland. J Bone Joint Surg 54B:13-17, Feb 1972
9. Le Damany P: La luxation congenitale de la hanche. Paris, Felix Alcan, 1912
10. Ortolani M: Un segno poco noto e sua importanza per la diagnosi precose di prelussazione congenita dell'anca. Pediatria 45:129, 1937
11. Von Rosen S: Early diagnosis and treatment of congenital dislocation of the hip joint. Acta Orthop Scand 26:242, 1961
12. Hilgenreiner H: Zur frühdiagnose and frühbehandlung der angeborenen Huftegelenkverrenkung. Med Klin 21:1385, 1925
13. Ramsey P, Lasser S, McEwen G: Congenital dislocation of the hip; use of the Pavlik harness in the child during the first six months of life. J Bone Joint Surg 58A:1000-1004, Oct 1976
14. Cyvin KB: Congenital dislocation of the hip joint; clinical studies with special reference to the pathogenesis. Acta Paed Scand [Suppl] (263):1-67, 1977
15. Valman HB: Congenital dislocation of the hip. Dev Med Child Neurol 20:103-104, 1978
16. Sharrard WJW: Neonatal diagnosis of congenital dislocation of the hip. Dev Med Child Neurol 20:389-390, 1978
17. Owen R: Congenital hip dislocation. Br Med J 3:370-371, Aug 1971

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Recent Advances in Antidepressant Drug Treatment

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Psychiatric research has made remarkable advances in understanding the pathophysiology of depressive illnesses. Biologic depressions are now understood as neurotransmitter deficiency diseases. Certain forms of depression are treated with tricyclic antidepressant drugs, which increase the amount of available neurotransmitters. Complicating the clinical picture, however, is the problem of wide variability of levels of tricyclic drugs in the plasma of persons receiving the same dosage. Another problem is the apparent linear dose-response relationship of imipramine hydrochloride and its sister compound desipramine hydrochloride while amitriptyline and nortriptyline follow an inverted U-shaped dose-response curve. However, with newer, more sophisticated diagnostic methods, combined with monitoring of tricyclic drug levels in plasma, therapeutic efficacy can approach 90 percent.

Available neurotransmitters also can be increased using monoamine oxidase (MAO) inhibitors. Although MAO inhibitors have been less popular than the tricyclic drugs, recent clinical research tends to support their efficacy. Distinct individual differences in the rate of metabolism of MAO inhibitors have been found. New methods are being devised to detect these differences and monitor directly the effects of these drugs. One of these methods, platelet MAO inhibition, shows some clinical promise.

Tricyclic drugs and MAO inhibitors have recently been joined by lithium carbonate, which shows notable efficacy in removing acute manic-depressive symptoms as well as preventing their return during maintenance treatment. Its utility in treating cyclic depressions without mania is now being explored by researchers.

TRICYCLIC ANTIDEPRESSANT drugs have been available for more than 20 years, but only relatively recently have they received widespread acceptance as clinically effective agents. Monoamine oxidase (MAO) inhibitor antidepressant drugs have been available somewhat longer but are still viewed as ineffective and potentially dangerous. It is not entirely clear why this has been so. Perhaps part of the explanation rests on the difficulties associated with making appropriate treatment-specific diagnoses. Not enough has been learned about the basic pathophysiology of the various depressive disorders. It is still debated, for ex-

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ABBREVIATIONS USED IN TEXT
ECT = electroconvulsive therapy
MAO = monoamine oxidase

ample, whether so-called neurotic depressive persons can be effectively treated with antidepressant drugs. However, fundamental gaps in our knowledge about the pharmacology of the antidepressant drugs have clearly been major stumbling blocks in their effective use. After arbitrarily choosing an antidepressant drug, physicians have been left with little more to guide their dosage regulation than their clinical experience. Unfortunately, often the only observable clue that a given drug is affecting the system has been the emergence of annoying side effects. More accurate information regarding tricyclic drug levels in blood is of utmost importance to clinicians. However, even today, few laboratories, outside research settings, can provide such information.

In contrast, a different course of events followed the introduction of lithium carbonate into the United States in 1971. From the diagnostic point of view, classic cases of mania present with readily diagnosable symptoms that sometimes literally scream out for treatment. The technical ease of monitoring levels of lithium carbonate in plasma has made it a very popular drug despite its fairly narrow therapeutic index.

This article reviews the clinically relevant literature concerning the tricyclic antidepressant drugs and the MAO inhibitors, with special emphasis on the newer methods of diagnosis and drug-level monitoring. Lithium carbonate and electroconvulsive therapy (ECT) also will be discussed as they relate to special types of depressions and drug treatment failures.

Theoretical Basis of Pharmacologic Action

The current etiologic theory of biologic depressions proposes a deficit of one or more central neurotransmitters. Originally labeled the catecholamine theory of depression, because of its focus on norepinephrine,[1,2] it now emphasizes the possible importance of low levels of other neurotransmitters such as the indolamine serotonin (5-hydroxytryptamine).[3-5] This theory points to deficient levels of serotonin as permitting the full manifestation of low norepinephrine levels in depression. Conversely, low serotonin, in the face of high norepinephrine, would express itself clinically as mania. This so-called permissive theory attempts to join unipolar depressions with bipolar (manic-depressive) depressions under a common biochemical defect. If correct, it might explain why manic-depressive patients in their depressed state are virtually indistinguishable from other depressive persons. The underpinnings of the neurotransmitter theories of depression rest on the observation that reserpine produces, in animals and man, psychomotor symptoms similar to those seen in clinical depression.[6] Examination of the brains of reserpinized animals shows a depletion of norepinephrine, serotonin and dopamine. Treatment with antidepressant drugs tends to restore these neurotransmitters to normal levels and removes the signs of psychomotor retardation.

Another, somewhat more dynamic theory suggests the existence of a critical balance of one or more neurotransmitter systems with acetylcholine. Just as the motor manifestations of parkinsonism are now seen as resulting from an imbalance of dopamine with respect to acetylcholine, depressive symptoms could be viewed as arising from lack of modulation of norepinephrine by acetylcholine.[7] Attempts to increase acetylcholine in manic patients by giving the cholinesterase inhibitor physostigmine have produced intriguing but inconsistent results. In some patients abrupt swings toward suicidal depression occurred, while in others there was only decreased motor activity.[8]

Tricyclic Antidepressant Drugs

Imipramine, the first tricyclic antidepressant drug, was discovered in the course of a search for a better chlorpromazine-like drug. While investigating the neuroleptic activity of imipramine, Kuhn[9] found that it was ineffective for the thought disorder of schizophrenics but produced improvement in depressed patients.

The commonly available tricyclic antidepressant drugs—imipramine, amitriptyline, desipramine, nortriptyline, protriptyline and doxepin—are structurally different from the phenothiazines only in apparently minor ways. For example, the sulfur atom in the phenothiazine molecule is replaced in the tricyclic drugs by a two-carbon or carbon-oxygen bridge. This similarity emphasizes the importance of minor structural changes in the production of critical differences in basic pharmacologic activity. The phenothiazines are thought to exert their antischizophrenic effect by dopamine-receptor blockade. The mechanism of action of the tricyclic drugs, as illustrated in Figure 1, is to increase the relative levels of neurotransmitter in

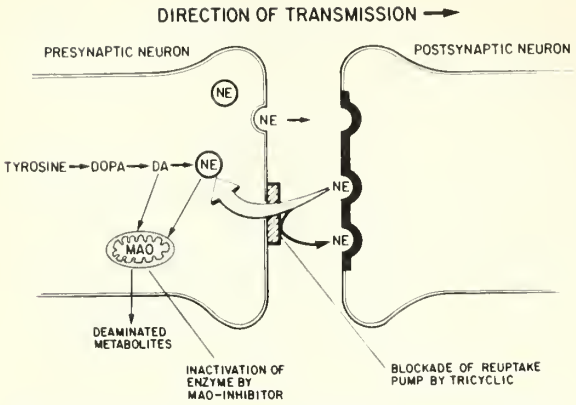

Figure 1.—Schematic representation of central norepinephrine (NE) nerve synapse. Note the pathways of neurotransmitter formation, release and reuptake. Partial inhibition of the reuptake pump by tricyclic antidepressant drug results in increased levels of transmitter capable of depolarizing the postsynaptic membrane. Inhibition of mitochondrial monoamine oxidase (MAO) leads to a build-up in precursors and stored neurotransmitter. (DA, dopamine.)

the synaptic cleft by blocking the presynaptic reuptake pump. Different tricyclic drugs vary in the degree to which they inhibit the reuptake of norepinephrine and serotonin. Desipramine acts almost exclusively on norepinephrine, while amitriptyline is most effective in blocking serotonin.[10]

Because tricyclic antidepressant drugs are quite lipid-soluble and therefore almost completely absorbed from the gastrointestinal tract, other routes of administration are unnecessary and are potentially hazardous. Once in the system, imipramine and amitriptyline are partially metabolized in the liver to their respective desmethyl derivatives—desipramine and nortriptyline. These active metabolites, in equilibrium with their parent compounds, undoubtedly contribute to the total antidepressant effect.

The pharmaceutical industry synthesized these derivatives in the hope that they might be found to exert their antidepressant action with a shorter lag period than their parent compounds. In numerous studies, however, no differences in onset of action or efficacy of any of the various tricyclic compounds have been found. One experimental tricyclic compound, amoxapine, does show a significantly shorter lag time but it apparently does not have increased overall efficacy when compared with standard tricyclic drugs.[11]

Clinical Effects

In nondepressed persons, tricyclic drugs produce varying degrees of sedation. In depressed patients, however, they produce striking improvement in negativistic ruminations, depressed mood and slowed motor behavior—generally with noticeable changes three to ten days after commencing treatment. These drugs cannot be termed psychostimulants, because they produce a normal mood rather than euphoria or hyperactivity. Controlled studies indicate that at least 70 percent of depressed patients are substantially benefited by tricyclic antidepressant drugs, while only 40 percent are helped by a placebo in the same period.[12]

Apparently there are populations of responders and nonresponders to the tricyclic antidepressant drugs (as well as to MAO inhibitors); therefore, the pretreatment determination of potential response to the available types of treatment is of great importance. Surprisingly few studies have claimed to identify variables associated with good drug response or subpopulations of depressed patients who are susceptible to specific types of antidepressant drugs. However, Pare and associates[13] argued that when a genetic relative of a patient has responded well to either MAO inhibitors or tricyclic medications, the patient may be expected to respond to the same class of medication or to a specific drug within a class. For example, it is not uncommon in clinical practice to find a patient who responds only to a specific tricyclic drug. There is often a good chance of finding other affected members of his family who have responded to the same drug. Consequently, valuable information regarding a patient's treatment can be uncovered by taking a careful family history.

Kiloh and associates[14] found that predictors of a positive response to imipramine are associated with more severe endogenous depressions. These endogenous or biologic symptoms typically present as early morning wakening, psychomotor retardation or agitation, weight loss, and overwhelming feelings of worthlessness and guilt. However, there tends to be a less favorable response to imipramine by patients with neurotic and characterological depressions whose premorbid personalities have included hypochondriacal, self-pitying and hysterical traits. Delusional patients, according to Horden and associates,[15] tend to have a poor response to imipramine. Glassman and coworkers[16] found that by excluding delusional depressive patients, the response rate with imipramine approached 85 percent. Good diagnosis, based on readily recordable signs and

symptoms, is becoming even more essential for definitive treatment.

Some investigators[17,18] have claimed that those depressed patients who show a transient elevation of mood when amphetamine is given, tend to respond better to imipramine than to amitriptyline. This encouraging finding should be carefully investigated since this simple pretreatment test could conceivably point the way toward placing the patient on the optimal drug and obviating the need to switch drugs during treatment.

Dosage

As has been stated above, dosage is increasingly recognized as an important factor in the drug treatment of depression. Many of the studies that have shown poor results with antidepressant drugs undoubtedly reflect the results of inadequate doses—either subtherapeutic amounts or too short a trial. Only after three to four weeks at adequate dosage can one be sure that unresponsive patients will not improve on a particular drug. Simply increasing the dosage may not be the final answer, however, as will be discussed in the next section on blood levels. Many psychiatrists favor dose levels of 150 mg to 250 mg per day of imipramine or amitriptyline—a level that should be achieved over a period of several days to a week. In contrast, other investigators feel that the ideal therapeutic dose lies between 50 mg and 600 mg per day.[19] Protriptyline seems to be an exception. It is more potent than the other tricyclic antidepressant drugs, and smaller daily doses of this drug are required. A study of protriptyline hydrochloride levels in blood indicated that the greater relative potency may be due to slower metabolism of the drug, since circulating levels are in the same range as those of other tricyclic antidepressant drugs.[20] Flexible dosage, within boundaries defined by known properties of the particular drug, will doubtless increase the response rate.

Blood Levels

Approximately 30 percent of depressed patients do not initially respond to tricyclic medication. Some of these patients appear to suffer from forms of depression that are not affected by tricyclic antidepressant drugs. Others do not respond because levels of the medication in the blood are either too low or too high for good therapeutic effect. This is due presumably to variations in the rate of metabolism.

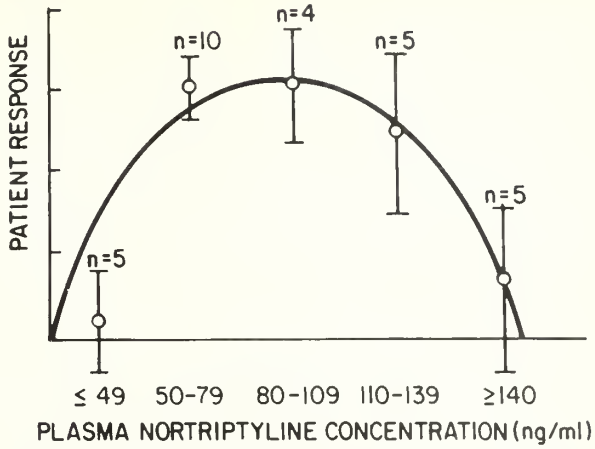

Figure 2.—Relationship between antidepressant response and steady-state plasma concentrations in 39 patients receiving 25 to 75 mg nortriptyline hydrochloride three times a day. Maximum benefit was found in the range of 50 to 139 ng per ml (adapted from Asberg et al[24]).

There are pronounced individual differences in levels of tricyclic drugs in plasma among patients given the same dosage—up to 40-fold in one study.[21] Once a maintenance dose is started, drug levels in the blood tend to build up over the course of a week until they reach equilibrium. However, some patients for various reasons have reduced metabolism or diminished blood and tissue binding capacity; normal doses of medication for these patients rapidly produce toxicity.

In other patients normal doses are metabolized so rapidly that effective tricyclic drug levels fail to develop in blood and brain. Studies of close relatives of patients in whom the drugs are metabolized either rapidly or slowly have shown that they also have unusual rates of drug metabolism.[22] Therefore, genetics plays an important role in this particular effect.

Rapid metabolism of tricyclic drugs may also result from simultaneous administration of drugs that cause induction of hepatic enzymes. It has been shown, for example, that phenobarbital reduces the levels of tricyclic drugs in plasma by approximately 50 percent.[23]

In studies by Asberg and associates[24] and Kragh-Sorensen and associates[25] the relationship between concentrations of nortriptyline in plasma and therapeutic response was carefully documented. As can be seen in Figure 2, among patients who failed to respond, there were those with very high and very low blood levels of nortriptyline. Reduction of dose for nonresponding patients with abnormally high concentrations, while in-

creasing the dose in patients with low levels, resulted in rapid response for a significant number of these subjects. It has been suggested that at abnormally high levels of nortriptyline, some paradoxical pharmacologic property supervenes to nullify the principal effect of the drug. The term therapeutic window has been coined to describe this inverted U-shaped dose-response curve.[26]

Braithwaite and associates[27] produced similar findings in their studies of levels of amitriptyline in plasma. Low plasma levels of both amitriptyline and nortriptyline were found to be ineffective, whereas moderate levels produced good therapeutic results. Gruvstad[28] reanalyzed these data and found a tendency for patients with elevated blood levels to have a poorer response than patients with intermediate levels. Some controversy, however, has arisen with the failure of other research groups to confirm these findings.[29,30]

Although the weight of evidence supports the concept of a therapeutic window for nortriptyline and possibly amitriptyline this may not be the case for imipramine. Glassman and associates[16] found that this tricyclic compound follows a more linear plasma-response relationship. This can be seen in Figure 3, which reports the correlation of imipramine (together with its active metabolite desipramine) with patient response.

In summary, preliminary clinical findings indicate that there can be pronounced individual differences in response to the various tricyclic antidepressant drugs. Response also appears to be a function of the concentration in the plasma of a given drug; nonresponse, in many cases, indicates overly high concentrations as well as inadequate concentrations. Adjustments of medications to achieve therapeutic blood levels currently must be based on clinical acumen until routine and readily available laboratory procedures are developed to accomplish the same results.

Maintenance Treatment to Prevent Recurrent Depression

It has been estimated that of persons who experience an acute depression nearly half will have a recurrence at some time in their lives. This relapse rate becomes much more frequent in some patients. For example, in a survey of nine controlled studies that examined the relapse rate of patients with recurrent depression during the first year of untreated follow-up, Kessler[31] reported a range of 36 percent to 91 percent with

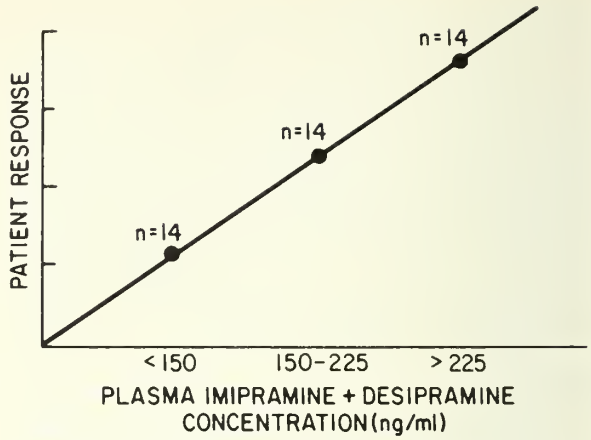

Figure 3.—Linear relationship of plasma level to antidepressant response in 42 patients receiving 100 to 300 mg of imipramine hydrochoride a day. Note that the combined plasma levels of imipramine hydrochloride and its desmethyl derivative, desipramine hydrochloride, are reported. The higher the plasma level of imipramine hydrochloride and desipramine hydrochloride the greater the fequency of response (adapted from Glassman et al[16]).

a mean of 64 percent. For many patients, then, maintenance treatment to prevent relapse gains central importance in therapy.

Recently, there have been three large collaborative studies concerning the role of maintenance therapy for patients initially treated with tricyclic drugs. Klerman and associates[32] studied 150 moderately ill depressive women, comparing the relative efficacy of maintenance on amitriptyline, individual psychotherapy and combination treatment. A no-pill, low-contact control group was included as well. At eight months, 36 percent of the control group, who received no treatment, had relapsed, while 12 percent of the drug therapy group and 16 percent of the psychotherapy group had relapsed. Relapses for the group who received combined drug therapy and psychotherapy did not differ significantly from those for groups on either drug therapy alone or psychotherapy alone.

A similar collaborative study was conducted by Mindham and associates[33,34] in Great Britain. After recovery, patients who were initially treated with tricyclic drugs were assigned randomly to either maintenance treatment (a reduced dosage of the tricyclic drug each had responded to) or placebo. A substantial prophylactic effect of the tricyclic drugs was shown. At the end of six months, approximately 50 percent of patients on placebo had relapsed compared with a relapse rate of 22 percent for patients on active medica-

tion. In a Veterans Administration collaborative study, Prien and associates[35] also compared imipramine with placebo and found that imipramine had significant prophylactic properties. In these severely ill patients in hospital, 92 percent relapsed on placebo compared with 48 percent who relapsed on drug treatment.

Davis[36] recommended maintaining the recovered patient for at least one month at full dosage before attempting a gradual stepwise reduction. Presumably those who relapse will do so less abruptly and can then be stabilized at a slightly higher dosage. Kragh-Sorensen and associates,[37] however, cautioned against arbitrary reduction in dosage from the level that was found to be effective in treating the acute episode. They pointed out that tricyclic drug levels are in stable equilibrium over time—neither inducing their own metabolism necessitating dosage increases nor accumulating in the body with adverse effects. Paykel and associates[38] found distinct advantage in maintaining patients on amitriptyline hydrochloride for eight months as compared with two months.

Clearly, some patients will never experience a recurrence of the original depression while others are in perpetual cycle of recurrent depression. Since there are no accurate predictors of relapse in the individual patient, except what is gathered from history, it is probably wise to treat most first-time depressions with maintenance medication for several months at a reduced dosage and most relapsing depressions with much longer stabilization at higher dosage.

For those patients who do not respond to tricyclic drugs or MAO inhibitors, or for those who are medically unsuitable for drug treatment, electroconvulsive therapy (ECT) is offered as an alternative. In a recent review of the efficacy of ECT, Davis and Ericksen[39] found an unusually high relapse rate in several studies. The rate was highest within the first few months after completion of treatment.

Two different investigations have sought to determine whether post-ECT relapse could be prevented by maintenance treatment with tricyclic drugs. Seager and Bird[40] employed a random assignment, double-blind design and followed post-ECT patients who received either placebo or imipramine for six months or until relapse occurred. The maintenance tricyclic medication had an impressive prophylactic effect: Of the group on imipramine maintenance, only 17 percent relapsed, whereas relapses occurred in 69 percent of the patients who received placebos. Following a similar design (post-ECT patients randomly assigned to receive amitriptyline or diazepam), Kay and associates[41] found that relapses occurred in a greater proportion of patients receiving diazepam than in the group receiving amitriptyline. Though neither of these studies of post-ECT patients involved large samples, the results were consistent in showing prophylactic properties for the tricyclic drugs. Because patients who are treated with ECT tend to be more profoundly depressed than others who receive drug therapy, they probably have a greater inherent tendency to relapse—and to relapse to the same level. It is therefore recommended that, whenever possible, ECT-treated patients should be given maintenance treatment with tricyclic drugs.

Treatment Combinations

Although not generally recommended in the literature, tricyclic antidepressant drugs can be safely combined with MAO inhibitors.[42,43] Whether this leads to enhanced efficacy is debatable, although most psychiatrists have had the experience of treating or seeing patients in whom remissions were achieved only with this combination.

Some interesting studies have shown an enhanced therapeutic response to the combination of imipramine hydrochloride with triiodothyronine. This effect is seen only in depressed women and not in men.[44] It also has been found that triiodothyronine alone has antidepressant properties, as does thyrotropin-releasing hormone.[45]

There is a loosely defined subpopulation of severely depressed patients who may benefit from a combination of antischizophrenic and antidepressant drugs. In my experience, family histories of these actively hallucinating persons occasionally include manic-depressive illness in close relatives; and such patients can benefit from treatment with lithium carbonate. If this fails, ECT is usually exceedingly beneficial and can be lifesaving in suicidal or very debilitated patients.

A common experience in evaluating patients who are unresponsive to treatment is the discovery that multiple drugs in irrational combinations have been administered, producing a toxic-confusional state or an atropine psychosis. Polypharmacy should be avoided if at all possible. Depressions tend to be time-limited, and medica-

tion side effects in many cases only complicate and prolong the natural course of the illness.

Lithium Carbonate

Lithium carbonate has gained a solid reputation in the treatment of bipolar manic-depressive illness. It is useful in the acute manic attack as well as in maintenance treatment to prevent further cyclic disturbances.[46,47] Moreover, some patients receiving maintenance treatment with lithium carbonate appear to benefit from a mild antidepressant action of the drug. These various effects naturally raise questions of whether lithium carbonate might be useful in treating other types of depression.

Unfortunately, lithium carbonate has been found to be a poor antidepressant medication in typical unipolar depression. Under active investigation, however, is its possible use in the prophylaxis of recurrent depression. A large collaborative study,[36] which examined this issue, showed that lithium carbonate has a somewhat limited effect in preventing further depressions; in nearly half of the patients relapse occurred within two years. In a recent follow-up of the original report, Prien and Caffey[48] suggested that higher levels of lithium in the serum produced acceptable prophylaxis. Patients with serum levels between 0.8 and 1.0 mEq per liter were as free from relapse as were those patients receiving imipramine in doses of 75 mg to 125 mg per day. However, patients with levels of 0.7 mEq per liter or less relapsed as frequently as did those patients receiving placebo. Because lithium carbonate typically must be taken several times a day and tricyclic drugs need to be taken only once a day, it might be difficult to convince patients to try maintenance with lithium carbonate without more specific indications. More research is needed in this area as well as in the area of the safety of lithium carbonate for long-term maintenance treatment. A disturbing report of possible nephrotoxicity involving lithium carbonate has caused many physicians to consider more carefully the reasons for prescribing this drug.[49]

Monoamine Oxidase Inhibitors

The first drugs with sustained antidepressant activity to be discovered were the monoamine oxidase (MAO) inhibitors. Although infrequently used today in general psychiatric practice, they are beginning to be reexamined for their possible therapeutic role in special clinical problems.

Iproniazid, the first MAO inhibitor, was originally used in the treatment of tuberculosis. Observers noted that in some of these patients iproniazid produced euphoria and mood elevation. Shortly afterward it was found that administration of this drug to more typical depressed patients produced favorable antidepressant results. Zeller and associates[50] established that the probable mechanism of action lay in the inhibition of the enzyme monoamine oxidase, resulting in an increase of neurotransmitters.

Monoamine oxidase is a ubiquitous enzyme that deaminates endogenously produced monoamines and monoamine-like substances acquired through food or drugs. In the central nervous system this mechanism helps to dispose of excess neurotransmitters. These neuronal monoamines (catecholamines and indolamines) are deaminated either before release or after reuptake by intraneuronal MAO located on the mitochondrial membrane, as shown in Figure 1.

Two classes of MAO inhibitors are in current use: the hydrazines and the nonhydrazines. The hydrazines (represented by phenelzine, nialamide and isocarboxazid) are structurally similar to iproniazid. They cause an irreversible inhibition; that is, new monoamine oxidase enzyme must be produced to restore the capacity to deaminate. Tranylcypromine is the only nonhydrazine MAO available at present for clinical use. It is similar to amphetamine in its structure and may produce some of its antidepressant effects by means of an amphetamine-like mechanism.[51]

Efficacy

Although MAO inhibitors have been available longer than tricyclic drugs, their efficacy is still questioned. A number of MAO inhibitors have been introduced and later withdrawn. Hepatotoxicity associated with iproniazid necessitated its early withdrawal, while other MAO inhibitors have been supplanted by newer agents because of lack of evidence that they were effective.

A growing body of literature shows that at least one MAO inhibitor, phenelzine, is effective. It is the only MAO inhibitor rated effective by the Food and Drug Administration. In their review of the efficacy studies, Robinson and associates[52] pointed to inadequate dosage as a principal reason for poor results with phenelzine. In their own double-blind study comparing phenelzine in a dosage of 60 mg per day with amitriptyline in a dosage of 75 mg per day there was rapid and

nearly identical improvement in both groups. This is the best evidence that an MAO inhibitor might be as effective as a tricyclic antidepressant drug.

Tranylcypromine is classified as an MAO inhibitor, although the appropriateness of this classification is in some doubt. In addition to MAO-inhibiting action, this agent may share some pharmacologic characteristics of the tricyclic drugs and amphetamines; that is, reuptake inhibition and direct agonist effects, respectively. Although tranylcypromine appears to be effective, studies have not been sufficient to permit a definitive statement.[53]

Evidence from double-blind studies leaves some doubt about the efficacy of isocarboxazid and nialamide. Negative results of these studies may derive from methodological insufficiencies, for example, underdosage or choice of inappropriate experimental population; however, the trend of the findings clearly raises questions about the effectiveness of these drugs.

Treatment of Atypical Depression With MAO Inhibitors

A number of reports suggest that MAO inhibitors may preferentially improve depressions with anxiety, phobic or other atypical features. In an early retrospective study of iproniazid, Alexander and Berkely[54] reported that neurotically depressed patients responded better (65 percent of 25 cases) than psychotic depressive patients (28 percent of 25 cases). Patients classified as having psychasthenic-anhedonic reaction responded fairly well (38 percent of 16 cases), while typical depressive patients responded poorly (26 percent of 38 cases). The most frequent complaints of patients who eventually responded were inability to work, fatigue, exhaustion, listlessness, not feeling well, unhappiness, being "down," inability to eat, diffidence and lack of self-confidence.

West and Dally[55] analyzed the symptoms of 101 depressed patients who were treated with iproniazid. A special group of atypical or hysterical depressive patients had the most rapid and unexpected responses. This form of depression was seen as a chronic condition with a high frequency of symptoms of fatigue, phobic anxiety and somatic complaints. Conversely, these depressions were not associated with classic endogenous symptoms such as early wakening, anorexia with weight loss, self-reproach and diurnal fluctuation in symptoms.

Robinson and associates[56] assessed the effects of phenelzine and placebo in a group of 88 outpatients with the diagnosis of depressive anxiety state. In contrast to the group receiving placebos, in the group receiving phenelzine there was significant improvement, which was most pronounced on dimensions of hypochondriasis, agitation, irritability and psychomotor change.

These studies suggest that MAO inhibitors may have special efficacy in those depressed patients who are often classified as neurotic. In these patients the most common symptom, besides depression, seems to be a great deal of somatization.

Treatment of Phobic Anxiety With MAO Inhibitors

In addition to their antidepressant effects, MAO inhibitors have been found effective in the treatment of phobic anxiety, as have the tricyclic antidepressant drugs. Kline[57] reported initial success with MAO inhibitors in cases of phobic-anxiety. Subsequently, Tyrer and associates[58] reported systematic, well-controlled studies in which phenelzine was significantly more effective than placebo in treating phobic-anxiety. Improvement often took up to two months to become manifiest. Consequently, these authors suggested that treatment regimens should allow for continuous treatment over a minimum of two months. The successful treatment of an individual phobic patient is illustrated in Figure 4. Details of this treatment will be discussed in the following section.

Biochemical Correlates of Effectiveness

MAO inhibitors affect the monoamine oxidase system throughout the body as well as in the central nervous system. There is the theoretical possibility that peripheral measurements of the inhibition of this enzyme could provide an indicator of central effectiveness. There are several reasons why this line of investigation might prove fruitful.

All persons seem to fall into one or the other of two genetically distinct groups according to the rate at which they metabolize certain drugs by acetylation. There are fast acetylators and slow acetylators. Since hydrazine MAO inhibitors are metabolized by acetylation, there is a distinct possibility that because of different acetylation rates some patients develop plasma levels of drug either too low or too high to be effective.[59] Nontherapeutic levels in plasma could develop even though patients were taking oral doses well within the recommended range.

Several investigative groups have measured

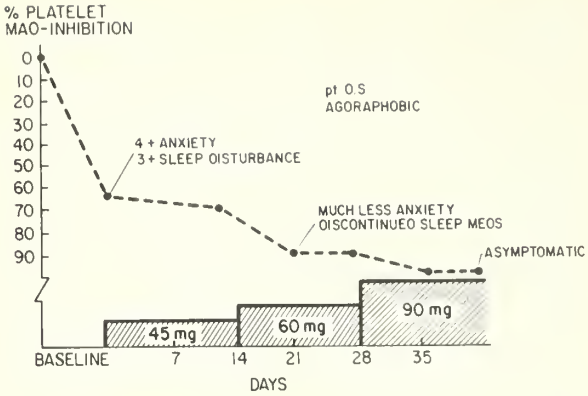

Figure 4.—Monoamine oxidase (MAO) inhibition as measured by percentage of platelet MAO inhibition in an agoraphobic patient receiving increasing doses of phenelzine sulfate. The patient showed improvement at 85 percent but at 90 percent cleared completely.

peripheral MAO inhibition in platelets from patients on phenelzine as an indirect measure of central MAO inhibition. Robinson and associates[60] reported a 68 percent improvement in depressed patients reaching 90 percent inhibition with phenelzine, whereas only 40 percent of patients improved at less than 90 percent inhibition. These authors suggested that an inhibition threshold may have to be exceeded before therapeutic benefit can be expected.

Figure 4 shows an example from a research study using an agoraphobic patient from the author's practice. Along the abscissa are graphed the oral dosages of phenelzine prescribed during treatment. The ordinate shows the percentages of MAO inhibition as measured from his platelets. This patient probably was a rapid acetylator; he did not obtain adequate MAO inhibition, and hence complete response, until the dose was pushed to a relatively high level.

Side Effects

The MAO inhibitors have a reputation for causing potentially dangerous hypertensive crises in the presence of sympathomimetic drugs or foods that contain tyramine. This reputation undoubtedly contributes to clinicians' lack of enthusiasm for MAO inhibitors. In actual practice, however, hypotension is a more frequent problem than hypertension. This is especially true at the start of treatment even with low dosage.

Patients taking MAO inhibitors should be carefully instructed to abstain from the following foods: pickled herring; chicken livers; wine, beer and sherry; aged cheeses, and the pods of broad beans.[61] Other foods that can be potentially interactive include figs, raisins, soy sauce, sour cream, bananas, sausages and coffee. Flushing of the skin and a mild headache are the most common reactions following consumption of one of the above foods. Many patients, however, are able to eat many of these foods without experiencing any side effects. Nevertheless, the strictest warnings must be given regarding the use of sympathomimetic medications and levodopa.

Another troublesome side effect that develops in many patients is the accumulation of interstitial fluid. This can be found in the form of dependent edema but also may be seen localized to one hand, or the face, if it has received recent trauma. The cause is not known but probably relates to subtle autonomic dysfunction in the peripheral circulation and should be viewed as an indication to lower the dosage.

Conclusions

- Research findings indicate that the efficacy of tricyclic antidepressant drugs can be increased by more accurate diagnosis and monitoring of treatment response. Determination of plasma levels eventually will give clinicians the needed information to adjust dosage for optimal response, but until that time, flexibility of dosage seems to be the best approach.
- Lithium carbonate shows unique properties in the treatment of bipolar (manic-depressive) patients. It may have a prophylactic effect in recurrent unipolar depressive disease as well, especially at higher plasma levels.
- Electroconvulsive therapy, long a mainstay of antidepressant treatment, is now most effectively utilized in the special cases of drug treatment failure. Maintenance treatment with tricyclic drugs for the post-ECT patient is the most rational approach to avoid relapse.
- As the efficacy of MAO inhibitors has been called into question, new evidence has emerged to support their usefulness. Better measures of adequate enzyme inhibition have shown that dosage has often been inadequate because of rapid acetylation in some patients.

REFERENCES

1. Bunney WE, Davis JM: Norepinephrine in depressive reactions. Arch Gen Psychiatry 13:483-494, 1965
2. Schildkraut JJ: The catecholamine hypothesis of affective disorders. Am J Psychiatry 122:509-522, 1965
3. Mendels J, Frazer A: Brain biogenic amine depletion and mood. Arch Gen Psychiatry 30:447-451, 1974
4. Asberg M, Thorin P, Traskman L, et al: "Serotonin depression"—A biochemical subgroup within the affective disorders? Science 191:478-480, 1976

5. Kety S, Ho BT, McIsaacs WM: Brain Chemistry in Mental Disease. New York, Plenum Press, 1971, p 237

6. Mendels J, Frazer A: Brain biogenic amine depletion and mood. Arch Gen Psychiatry 30:447-451, 1974

7. Janowsky DS, El-Yousef MK, Davis JM, et al: A cholinergic-adrenergic hypothesis of mania and depression. Lancet 2:632-635, 1972

8. Janowsky DS, El-Yousef MK, Davis JM, et al: Parasympathetic suppression of manic symptoms by physostigmine. Arch Gen Psychiatry 28:542-547, 1972

9. Kuhn R: The treatment of depressive states with G 22355 (imipramine hydrochloride). Am J Psychiatry 115:459-464, 1958

10. Hollister LE: Tricyclic antidepressants (first of two parts). New Engl J Med 299:1106-1109, 1978

11. Donlon PT, Biertuempfel HC: Oral communication. Oct, 1978

12. Klein DF, Davis JM: Diagnosis and Drug Treatment of Psychiatric Disorders. Baltimore, Williams & Wilkins, 1969, p 194

13. Pare CMB, Rees L, Sainsbury MJ: Differentitation of two genetically specific types of depression by the response to antidepressants. Lancet 2:1340, 1962

14. Kiloh LG, Ball JRB, Garside RF: Prognostic factors in treatment of depressive states with imipramine. Br Med J 1: 1225-1227, 1962

15. Horden A, Burt CG, Holt NF: Depressive States. Springfield IL, Charles C Thomas, 1965

16. Glassman AH, Perel JM, Shostak M, et al: Clinical implications of imipramine plasma levels for depressive illness. Arch Gen Psychiatry 34:197-203, 1977

17. Fawcett J, Siomopoulus V: Dextroamphetamine response as a possible predictor of improvement with tricyclic therapy in depression. Arch Gen Psychiatry 25:247-255, 1971

18. Van Kammen DP, Murphy DL: Prediction of imipramine antidepressant response by a one-day d-amphetamine trial. Am J Psychiatry 13:1179-1184, 1978

19. Schuckit MA, Feighner JP: Safety of high-dose tricyclic antidepressant therapy. Am J Psychiatry 128:1456-1459, 1972

20. Biggs JT, Holland WH, Sherman WR: Steady-rate protriptyline levels in an outpatient population. Am J Psychiatry 132:960-962, 1975

21. Hammer W, Sjoqvist F: Plasma levels of monomethylated tricyclic antidepressants during treatment with imipramine-like compounds. Life Sci 6:1895-1903, 1967

22. Asberg M, Price-Evans D, Sjoqvist F: Genetic control of nortriptyline kinetics in man: A study of relatives of patients with high plasma concentrations. J Med Genet 8:129-135, 1971

23. Hammer W, Idestrom CM, Sjoqvist F: Chemical control of antidepressant drug therapy, *In* Anti-Depressant Drugs, Excerpta Medica Int Congr Series 122. Amsterdam, Excerpta Medica, 1967, pp 301-310

24. Asberg M, Cronholm B, Sjoqvist F, et al: Relationship between plasma levels and therapeutic effect of nortriptyline. Br Med J 3:331-334, 1971

25. Kragh-Sorensen P, Asberg M, Eggert-Hansen C: Plasma nortriptyline levels in endogenous depression. Lancet 1:113-115, 1973

26. Davis JM, Ericksen S, Dekirmenjian H: Plasma levels of antipsychotic drugs and clinical response, *In* Lipton MA, DiMascio A, Killam KF (Eds): Psychopharmacology: A Generation of Progress. New York, Raven Press, 1978, p 906

27. Braithwaite RA Goulding R, Theano G, et al: Plasma concentration of amitriptyline and clinical response. Lancet 1:1297-1300, 1972

28. Gruvstad M: Plasma levels of antidepressants and clinical response. Lancet 1:95-96, 1973

29. Coppen A: Amitriptyline plasma concentration and clinical effect. Lancet 1:63-66, 1978

30. Robinson DS, Nies A, Copper TB: Tricyclic plasma levels in depressed outpatients. Scientific Proceedings, 131 Annual Meeting of the American Psychiatric Association, Atlanta, 1978, p 47

31. Kessler KA: Tricyclic antidepressants: Mode of action and clinical use, *In* Lipton MA, DiMascio A, Killam KF (Eds): Psychopharmacology: A Generation of Progress. New York, Raven Press, 1978

32. Klerman GL, DiMascio A, Weisman M, et al: Treatment of depression by drugs and psychotherapy. Am J Psychiatry 131: 186-191, 1974

33. Mindham RHS, Howland C, Shepherd M: Continuation therapy with tricyclic antidepressants in depressive illness. Lancet 2:854-855, 1972

34. Mindham RHS, Howland C, Shepherd M: An evaluation of continuation therapy with tricyclic antidepressants in depressive illness. Psychol Med 3:5-17, 1973

35. Prien RF, Klett CJ, Caffey EM: Lithium carbonate and imipramine in prevention of affective episodes. Arch Gen Psychiatry 29:420-425, 1973

36. Davis JM: Tricyclic antidepressants, *In* Simpson LL (Ed): Drug Treatment of Mental Disorders. New York, Raven Press, 1976, p 133

37. Kragh-Sorensen PK, Hansen E, Baastrup PC, et al: Self-inhibiting action of nortriptylin's antidepressive effect at high plasma levels: A randomized, double-blind study controlled by plasma concentrations in patients with endogenous depression. Psychopharmacologia 45:305-312, 1976

38. Paykel ES, DiMascio A, Haskell D, et al: Effects of maintenance amitriptyline and psychotherapy on symptoms of depression. Psychol Med 5:67-77, 1975

39. Davis JM, Ericksen SE: Efficacy of ECT in depression, *In* Audrey J (Ed): ECT: Efficiency and Impact. New York, Academic Press, (In press)

40. Seager CP, Bird RL: Imipramine with electrical treatment in depression controlled trial. J Ment Sci 108:704-707, 1962

41. Kay DWK, Fahy T, Garside RF: A seven-month double-blind trial of amitriptyline and diazepam in ECT-treated depressed patients. Br J Psychiatry 117:667-671, 1970

42. Shuckit J, Robins E, Feighner J: Tricyclic antidepressants and monoamine oxidase inhibitors—Combined therapy in the treatment of depression. Arch Gen Psychiatry 24:509-514, 1971

43. Pare CMB: Introduction to clinical aspects of monoamine oxidase inhibitors in the treatment of depression, *In* Ciba Foundation Symposium 39: Monoamine Oxidase and Its Inhibition. New York, Elsevier/Excepta Medica/North Holland, 1976, p 278

44. Wilson IC, Prange AJ Jr, Lara PP: L-triiodothyronine alone and with imipramine in the treatment of depressed women, *In* Prange AJ Jr (Ed): The Thyroid Axis, Drugs and Behavior. New York, Raven Press, 1974, pp 49-62

45. Prange AJ Jr, Wilson IC, Lara PP, et al: Effects of thyrotropin-releasing hormone in depression, *In* Prange AJ Jr (Ed): The Thyroid Axis, Drugs and Behavior. New York, Raven Press, 1974, pp 135-145

46. Davis JM: Overview: Maintenance therapy in psychiatry: II. Affective disorders. Am J Psychiatry 133:1-13 1976

47. Prien RF, Caffey EM Jr, Klett CJ: Factors associated with lithium responses in the prophylactic treatment of bipolar manic-depressive illness. Arch Gen Psychiatry 31:189-192, 1974

48. Prien RF, Caffey EM Jr: Relationship between dosage and response to lithium prophylaxis in recurrent depression. Am J Psychiatry 133:567-570, 1976

49. Hestbech H, Hansen HE, Amdisen A, et al: Chronic renal lesions following long-term treatment with lithium. Kidney Inter 12:205-213, 1977

50. Zeller EA, Barsky J, Fouts JR, et al: Influence of isonicotinic acid hydrazide (INH) and 1-isonicotiny-2-isopropyl hydrazine (IIH) on bacterial and mammalian enzymes. Experientia 8::349, 1952

51. Simpson LL, Cabot B: Monoamine oxidase inhibitors, *In* Simpson LL (Ed): Drug Treatment of Mental Disorders. New York, Raven Press, 1976, p 152

52. Robinson DE, Nies A, Ravaris CL, et al: Clinical psychopharmacology of phenelzine: MAO activity and clinical response, *In* Lipton MA, DiMascio A, Killam KF (Eds): Psychopharmacology: A Generation of Progress. New York, Raven Press 1978

53. Atkinson RM, Ditman KS: Tranylcypromine: A review. Clin Pharmacol 6:631-655, 1965

54. Alexander L, Berkely AW: The inert psychasthenic reaction (anhedonia) as differentiated from classic depression and its response to iproniazid. Ann NY Acad Sci 80:669-679, 1959

55. West EM, Dally PJ: Effects of iproniazid in depressive syndromes. Br Med J 1:1491-1494, 1959

56. Robinson DS, Nies A, Ravaris L, et al: The monoamine oxidase inhibitor phenelzine, in the treatment of depressive-anxiety states. Arch Gen Psychiatry 29:407-413 1973

57. Kline NS: Drug treatment of phobic disorders. Am J Psychiatry 123:1447-1450, 1967

58. Tyrer P, Candy J, Kelly D: Phenelzine in phobic anxiety: A controlled trial. Psychol Med 3:120-124, 1973

59. Evans DAP, Davison K, Pratt RTC: The influence of acetylator phenotype on the effects of treating depression with phenelzine. Clin Pharmac Ther 6:430-435, 1965

60. Robinson DS, Nies A, Ravaris CL, et al: Acute versus chronic effects of monoamine oxidase inhibitors in depressed patients: Time course of MAO inhibitors. Psychopharmacol Bull 13:50-51, 1977

61. Sen NP: Analysis and significance of tyramine in foods. J Food Sci 34:22-26, 1969

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The Relative Contributions of Nature and Nurture in Chronic Obstructive Pulmonary Disease

Chronic bronchitis with its accompanying emphysema is a disease on which a good deal of wholly unmerited sympathy is frequently wasted. It is a disease of the gluttonous, bibulous, otiose, and obese and represents a well-deserved nemesis for these unlovely indulgences . . . the majority of cases are undoubtedly due to surfeit and self-indulgence.

LEONARD LLEWELLYN B. WILLIAMS, 1925[1]

THERE IS LITTLE DOUBT that chronic obstructive pulmonary disease (COPD) has multifactorial origins.[2-4] Exactly what factors are involved and how they are related is, however, still unclear. This review examines the evidence relating to various putative risk factors to see whether this information can be used to develop a profile of high-risk persons.

Terminology, Definitions and Diagnosis

The term chronic obstructive pulmonary disease is commonly used to lump together four distinct conditions: chronic bronchitis, emphysema, asthma and bronchiectasis. These conditions have very different structural characteristics, different natural histories and often different causes. They are lumped together because they share many features that are often hard to separate clinically and because they share a common physiologic manifestation, airflow obstruction. This review focuses on two of these conditions: chronic bronchitis and emphysema.

Chronic bronchitis is defined in clinical terms as a disorder characterized by excessive production of mucus in the bronchial tree and manifested by chronic or recurrent productive cough, which is present on most days for a minimum of three months in the year and for no less than two successive years.[5]

Emphysema is defined in structural terms as a condition of the lung characterized by abnormal enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls.[5]

From these definitions, it is clear that the structural changes that accompany both chronic bronchitis and emphysema can cause airflow obstruction. In chronic bronchitis, for example, airflow obstruction is a consequence of the presence of excessive amounts of mucus in both large (inside diameter greater than 2 mm) and small (inside diameter less than 2 mm) airways and of the inflammatory changes that cause severe structural narrowing and distortion in a large proportion of the small airways.[6] In emphysema, airflow obstruction is often a consequence of the loss of lung elastic recoil. The normal tethering action of the alveolar walls is impaired as alve-

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ABBREVIATIONS USED IN TEXT

α_1AT = alpha$_1$-antitrypsin
COPD = chronic obstructive pulmonary disease
FEV$_1$ = one-second forced expiratory volume
FVC = forced vital capacity
RSV = respiratory syncytial virus

olar walls are destroyed; and, as a result, the airways collapse at a higher than normal transpulmonary pressure.

The extent of airflow obstruction can most readily be shown by spirometry (Figure 1). Although spirometric tests are generally too insensitive to detect early physiologic changes of airflow obstruction, which in cigarette smokers are probably caused by obstruction in small airways,[7] they are adequate for clinical use and may be as useful as the newer tests of small airway function in identifying the smoker who will progress to clinical airflow obstruction.[8,9]

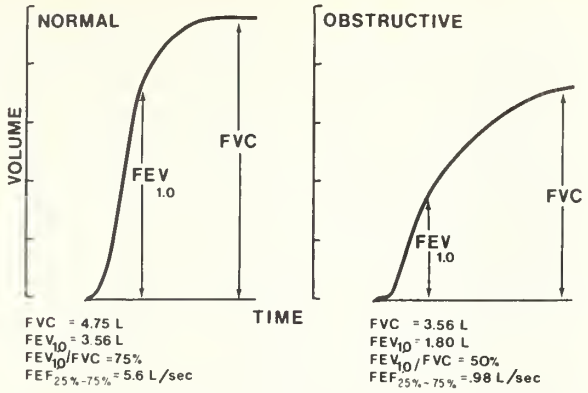

Figure 1.—Spirograms from a normal person (left) and a smoker with airflow obstruction (right). In the smoker, one-second forced expiratory volume (FEV$_1$), one-second forced expiratory volume to forced vital capacity ratio (FEV$_1$/FVC) and forced expiratory flow, 25% to 75% air expiration measurement (FEF$_{25\%-75\%}$) are all abnormally low.

Causes of COPD

Although some of the morphologic changes of emphysema were described as early as 1721[10] and the first clinical description of bronchitis was probably that of Sydenham, published in 1676,[11] clues about the causes of these conditions were very slow to emerge. The factors that have been linked most convincingly with chronic bronchitis and emphysema are heredity, smoking, childhood influences, air pollution and occupation. With the exception of cigarette smoking, however, it is not clear whether the associations are causal.

Heredity

The concept of hereditary factors in emphysema dates back to the early 1800's[12] and can be found in Sir William Osler's textbook, *The Principles and Practice of Medicine,* sixth edition, published in 1905.[13] Many recent reports suggest that hereditary factors are implicated in COPD.[14-18] Many of these clinical case reports have dealt with single kindreds or family histories of patients found to have COPD. Studies using strict epidemiologic criteria for population selection and data collection have only recently been undertaken.[19-22] These studies have shown that genetic factors contribute to normal lung function and that COPD shows familial aggregation. Higgins and Keller[19] surveyed 9,226 residents of Tecumseh, Michigan, (82 percent of the population) and found that there were statistically significant correlations between the ventilatory function of parents and their offspring (less than 40 years of age). In general, the correlations were greater for children less than 16 years old than for offspring aged 16 to 39 years. Furthermore, the correlations were greater within the sexes (fathers and sons, mother and daughters) than between the sexes.

Familial aggregation for COPD has been shown in two large-scale epidemiologic studies. In the study quoted above,[19] Higgins and Keller found familial clustering of chronic bronchitis, asthma and allergic rhinitis in the Tecumseh population. However, there was also a familial resemblance in smoking habits, which makes it difficult to evaluate these data. In a similar study, Cohen and co-workers,[20,21] using a modified case-control design in Baltimore, found that relatives of patients with COPD had a higher prevalence of function impairment (as shown by one-second forced expiratory volume [FEV$_1$]) than did appropriately selected control groups that consisted of relatives of nonpulmonary patients, neighbors and an occupational sub-group (teachers), after adjusting for age, sex, race and smoking habit. Furthermore, when Cohen and associates included patients with COPD and their first-degree relatives in the study, they found a higher prevalence of function aberrancy in those with blood group A than in those with blood group B, providing additional evidence that function level has an important genetic determinant.

These findings provide firm evidence for a familial component in COPD but do not provide any clues as to the nature of the familial suscep-

tibility. The only genetically determined factor to be linked conclusively with COPD is alpha$_1$-antitrypsin (α_1AT) deficiency, described first by Laurell and Eriksson in 1963.[23] This condition has an autosomal recessive pattern of inheritance, with at least 23 co-dominant alleles,[24-26] and typically presents with shortness of breath in early adult life due to extensive panlobular emphysema. The destruction of lung parenchyma in this condition is probably due to the unopposed action of proteolytic enzymes released from disintegrating macrophages and leukocytes when there are inadequate levels of antiproteases in the blood.

Smoking

There is unequivocal evidence that cigarette smoking is related to chronic bronchitis and emphysema.[2-4] It is surprising, however, to realize that this association, though first suspected almost 90 years ago,[27] received little attention until the 1950's when a number of studies[28-34] showed that chronic cough and production of sputum, characteristic of chronic bronchitis, and symptoms and function impairment thought to be characteristic of emphysema[33,35,36] were more prevalent in smokers than in nonsmokers.

Subsequently, many studies carried out in the 1950's and early 1960's showed that smokers, especially those more than 40 years of age, had impairment of lung function when compared with nonsmokers.[30,37-44] The evaluation of new tests of small airway function, such as closing volume and the slope of the alveolar plateau (phase III) of the single breath N_2 test, introduced in the late 1960's, further confirmed and extended these observations.[45-47] From these studies and later studies that considered general population samples,[48,49] it became evident that up to a third of cigarette smokers in a general population sample will show evidence of impairment of lung function. Figure 2 illustrates findings of one such study carried out in adults aged 25 years through 54 years living in Montreal, Portland, Oregon, and Winnipeg.[49] Similar data have been reported from a recent large-scale study carried out in Tucson.[48]

These and other population surveys have clearly shown that a modest proportion of cigarette smokers have some impairment of lung function and that respiratory symptoms are much more prevalent in smokers than in nonsmokers. These studies do not, however, provide much information about the nature of the association

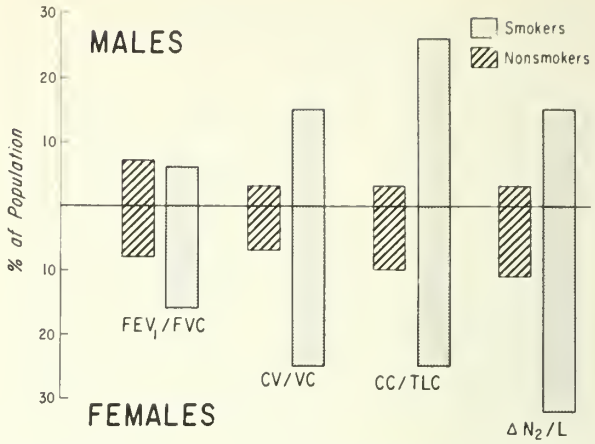

Figure 2.—Proportion of nonsmokers and smokers with abnormal tests in a 3-cities survey carried out in random population samples in Montreal, Portland, Oregon, and Winnipeg in 1974, involving a total of 332 nonsmokers (107 men, 225 women) and 491 smokers (267 men, 224 women). Abnormal tests defined as one-second forced expiratory volume to forced vital capacity ratio (FEV$_1$/FVC) more than 2 standard errors of estimate below the appropriate value for healthy nonsmokers and a closing volume to vital capacity ratio (CV/VC), closing capacity to total lung capaiity ratio (CC/TLC) and slope of the phase III of the single breath N_2 test (ΔN_2/L) more than 2 standard errors of estimate above the predicted value for healthy nonsmokers. Predicted values used were those developed in the study.[49]

nor do they provide insight into the natural history of the disease process. For these, one must turn to longitudinal studies.

Of the longitudinal studies that have been carried out over the past 15 years,[50-54] most have reported declines in function with age in smokers and nonsmokers similar to those predicted on the basis of regressions constructed from cross-sectional studies.[55-58] Although there is contradictory evidence about the aging model in both nonsmokers and smokers (linear or exponential), there is a clear consensus that smokers show a greater decline in function with age than do nonsmokers. However, if the frequency distribution of the decline in function is examined, it becomes apparent that most smokers show declines in function with age very similar to those seen in nonsmokers and only a small proportion of smokers show a very rapid decline. Such findings are illustrated in Figure 3, which shows the frequency distribution of the change in FEV$_1$ over five to six years in 342 nonsmokers and smokers, aged 16 years to 87 years, in a follow-up study[59] of a subgroup of subjects first tested at an emphysema screening center in Portland, Oregon, in 1971 and 1972. The study was designed to ob-

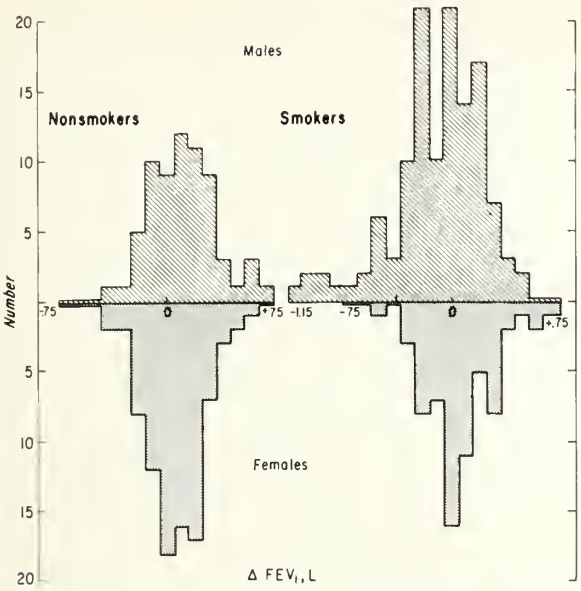

Figure 3.—Distribution of total change in one-second forced expiratory volume (FEV) over five to six years in 342 nonsmokers and smokers in a follow-up study[59] of a population who attended an emphysema screening center in 1971 and 1972. The population is divided by smoking habit and sex.

tain further information about the natural history of early airflow obstruction, so the subgroup used for the follow-up excluded all persons with an abnormal FEV_1.

This study[59] illustrates two points: (1) that only a small proportion of smokers show a rapid decline in function, as measured by FEV_1; and (2) that there seems to be a definite sex difference in that the persons who had a rapid decline in FEV_1 were all men. In the same study, nine persons, all male smokers (7 percent of the male smokers), progressed from a normal to an abnormal FEV_1 (more than 2 standard errors of estimate below the predicted values of Morris and co-workers[55]). No doubt this number will increase as the follow-up period is extended, but probably in only a small proportion of the smokers will clinical airflow obstruction, defined in terms of abnormal FEV_1, ever develop. These observations are very similar to those reported by Fletcher and co-workers,[52] who studied a group of 792 working men in London for eight years. Although longitudinal studies, such as the one described above, are able to provide some insight into the natural history of the disease process, they have not yet identified the nature of the association between smoking and chronic airflow obstruction. A simple dose-response relationship, one explanation, has been found by a number of investigators.[60-62] Many others, however, have failed to find a dose-response relationship;[41,49,63] and this does not appear to account for the different rates of decline either in the Portland study,[59] referred to above, or in Fletcher's study.[52] It may be that information about cigarette smoking is too inadequate to provide good quantitative data on total dose or site of deposition because these both depend heavily on methods of smoking. Pipe and cigar smokers do not appear to be at increased risk of developing COPD.

Childhood Influences

The idea that the seeds of chronic airflow obstruction are sown in childhood is not new. Several epidemiologic studies carried out in the United Kingdom between the late 1950's and early 1970's showed an association between childhood respiratory problems and bronchitis in adult life.[64-68] Caution must be used in interpreting the results of these studies, however, because they are so susceptible to recall bias; persons with a respiratory condition tend to have an increased awareness of respiratory symptoms and are therefore more likely to recall episodes of respiratory disease in childhood than are adults without a respiratory condition. The same problem holds for adults answering questionnaires on behalf of their children; the adult with respiratory symptoms is more likely to be aware of respiratory symptoms in a child. Recall bias is an important consideration in all studies that use a questionnaire as a measurement tool.

Additional evidence that childhood respiratory infections affect lung function in adult life has been reported by Burrows and associates[69,70] from a longitudinal epidemiologic study of a general population sample living in Tucson, Arizona. Of 2,626 subjects aged 20 years and older in the study, 416 (16 percent) claimed to have had respiratory trouble before age 16 years. Most of this respiratory trouble fell in the class of bronchitis or recurrent airways disease; a small proportion of the subjects reported only a severe acute illness such as pneumonia, croup or whooping cough. There was a higher frequency of almost all respiratory symptoms and diseases, physician-diagnosed chronic bronchitis and emphysema and abnormal pulmonary function tests in the group with childhood respiratory trouble than in the rest of the population studied. These differences were most evident in the nonsmokers

and were not accounted for by age. A history of pediatric respiratory illness was associated with mild impairment of ventilatory function in young adults, but persons with such a history showed an excessive decline in function with advance of age and cigarette use.

Whether all respiratory infections in early childhood are liable to leave residual damage or whether specific infectious agents are involved is not clear. There is some evidence to show that respiratory syncytial virus (RSV) is particularly likely to result in permanent structural changes and function impairment in a high proportion of children who are infected.[71] This becomes an important issue because RSV infection is a common cause of lower respiratory infection in children less than 6 months old. There is also evidence that only lower respiratory infections are important in terms of residual damage.[68]

The implications of the association between childhood respiratory tract infections and susceptibility to COPD in adult life are clear and important. If subsequent studies confirm this association, we will have a rational approach to the problem of prevention.

Other factors in childhood have been implicated in causing respiratory impairment. Socioeconomic status, family size, parental smoking, area of residence (pollution index) and method of cooking and heating[64,68,72] have been shown to influence the prevalence of respiratory symptoms and lung function impairment in children. Unfortunately, most of these factors are so closely linked that it has been very difficult to separate out the important, possibly causative factors from those that are spuriously linked. Also, because many of the data have been gathered in cross-sectional studies, it is difficult to establish causal relationships. Despite the shortcomings of the cross-sectional studies, they do provide a very important first step in data collection from which hypotheses can be generated and studies constructed.

In addition to the cross-sectional studies, there has been one longitudinal study[68]: a 20-year follow-up of 3,899 members of a cohort born in the United Kingdom in March 1946. In this group at age 20 years, cigarette smoking was found to have the greatest effect on symptom prevalence, followed by a history of lower respiratory tract illness before age 2 years. Social class and air pollution were found to have little effect. This study illustrates the importance of using longitudinal studies to confirm observations made from cross-sectional studies.

Air Pollution

Discovering the nature of the relationship between air pollution and COPD has been very difficult. There is unequivocal evidence that acute episodes of pollution—such as those that have occurred in London,[73] New York City,[74] Donora, Pennsylvania,[75] and the Meuse Valley in Belgium[76]—have been responsible for increased mortality and morbidity, primarily in persons who were already incapacitated with chronic heart or lung disease. There is much more uncertainty about the long-term effects of sustained low levels of pollutants, and many of the studies that have investigated this problem have failed to take into account smoking and occupation.

One approach that is usually not confounded by smoking is to study young school children who are exposed to different levels and types of air pollution. These studies have demonstrated differences in the frequency of lower respiratory tract infections and function level[68,77,78] corresponding to levels of air pollution. However, because it is not always possible to completely remove potentially confounding effects such as socioeconomic status, these studies should be interpreted with caution.

Another approach is to look for differences in healthy nonsmokers who are exposed to widely varying levels and types of air pollution. An example of this approach is a recent study,[49] of population samples in Montreal, Portland, Oregon, and Winnipeg, three North American cities with different air pollution levels and constituents. In this study, healthy nonsmokers were found to be very similar in terms of the relationship between both spirometric and single breath N_2 test variables and age; there was no evidence of a difference in either function level or the aging effect in the populations from the three cities. From this, one might conclude that, within certain limits, air pollution has little permanent effect on function level in healthy nonsmokers.

In persons with impaired lung defense mechanisms, be they smokers or nonsmokers, the situation may be entirely different, and it becomes virtually impossible to separate the effects of smoking, air pollution, occupation and other potentially confounding factors. In its recent review of the evidence relating to the effects of air pollution on health, a special committee of the

American Thoracic Society stated[79]: "the health community is hard pressed to reach consensus on the pollutant concentration that may increase the risk of chronic respiratory disease. The evidence is qualitative at best, i.e., heavy concentrations of sulfur oxide/particulate pollution appear to increase the public health risk of chronic respiratory disease, smoking is a dominant factor in the etiology of this disease, and air pollution probably adds a small part to the overall risk of the disease." It is likely that, in the presence of impaired lung defense mechanisms, air pollution acts in some synergistic way with cigarette smoke to aggravate hypersecretion of mucus and, in susceptible persons, to cause impairment of respiratory function.

Occupation

There are many opportunities for encountering respiratory tract irritants in the work place. The importance of dust exposure in relation to chronic respiratory disease was recognized in the early 1700's by Ramazzini and was subsequently emphasized by early clinicians.[80,81]

The problems arise in trying to separate the contribution of occupation from the many other possible confounding factors, such as environmental air pollution, smoking and socioeconomic status. Mortality statistics support the belief that occupation is a factor in chronic respiratory disease,[82,83] and cross-sectional studies of occupational groups strongly suggest that respiratory symptoms are more frequent in persons who are exposed to a wide variety of dusts and irritant gases than in individuals who work in relatively pollution-free environments. Whether there is progressive impairment of function is not clear, although there is some evidence from longitudinal studies to support this point of view.[84,85]

It may well be, as proposed for air pollution, that a wide variety of occupational irritants cause hypersecretion of mucus and therefore chronic cough and production of sputum, but that in healthy nonsmokers there is no appreciable impaired function nor is there a faster than expected decline in function with age. In smokers and nonsmokers who have impaired lung defenses, occupational irritants may act additively or multiplicatively to cause impaired function and a faster than expected decline in function with age.

This may not hold for all occupational exposures, however, and it seems likely that the responses in both nonsmokers and smokers depend on the nature of the occupational exposure and on the susceptibility of the individual worker. For example, Bouhuys and Van de Woestijne[86] have postulated that the function impairment observed in cotton workers may reflect both bronchoconstriction induced by the inhaled hemp dust and a mechanical or reflex effect of hemp on the larger airways. For the progressive airflow obstruction of byssinosis to develop in a cotton worker, therefore, there must be both the inhalation of hemp dust and a susceptible person. However, it has been estimated that 65 percent to 75 percent of the work force are reactors, or susceptible. This is not to say that disease develops only in susceptible workers. Indeed, there is good evidence that all cotton workers, whether smokers or nonsmokers, are affected to some degree by their work environment[86-89]—either with chronic respiratory symptoms or with airflow obstruction suggestive of small airway disease or both.

It is impossible to lump all occupations together when studying the contribution of the work environment to COPD. Much must be learned about which work environments are potentially hazardous and why and about the mechanisms whereby specific agents affect the lungs.

Identifying the High-Risk or Susceptible Smoker

It would be very helpful for the clinician to be able to identify the characteristics of the high-risk or susceptible smoker. In practical terms, it would mean that intensive efforts to encourage smoking cessation could be directed specifically at this group, as efforts are now made to modify the life styles of persons at high risk for coronary artery disease. This would not dilute or reduce general education about the deleterious effects of smoking on many organ systems.

Is enough known about the susceptible smoker to make this approach feasible? Unfortunately, the answer is no. The only factor linked causally to chronic airflow obstruction is cigarette smoking. The other factors discussed appear to be linked, but their exact roles are not yet understood.

Is there then a way in which the clinician can predict outcome in an individual smoker? From the longitudinal studies of Fletcher and associates in London working men,[8] Bates and co-workers in Canadian veterans[9] and the follow-up study of a screening center population in Portland,[59] two characteristics emerge that are of practical value

in identifying the smoker who is going to develop clinical airflow obstruction: (1) a function level that is low in relation to the predicted value for sex and age in early or midadult life, and (2) a more rapid than usual annual decline in function. Obviously, the latter requires measurements over time, probably two or three years, to separate the individual who is showing a relentless downward trend from the one who has labile function, usually due to some degree of reactive airway disease.

What tests can be used to identify the high-risk smoker? From the experience of the longitudinal studies, it appears that certain spirometric measurements are adequate for identification of the smoker who may develop clinical airflow obstruction. These spirometric measurements include one-second forced expiratory volume (FEV_1), the ratio of FEV_1 to forced vital capacity (FEV_1/FVC) and maximum midexpiratory flow. Thus, a value for any one or more of these variables that is in the low normal range (or is definitely abnormal) before a patient is 45 years old should alert the clinician that this person may fall into the high-risk category. The next step is to follow this person with annual or semiannual spirometric tests to observe the trend. An annual decline in FEV_1 of 15 to 40 ml in nonsmokers is predicted on the basis of cross-sectional studies[55-58] and has been observed in longitudinal studies.[50-56] Most smokers will also fall in this range. The smoker in whom clinical airflow obstruction is going to develop, on the other hand, must lose FEV_1 considerably faster for an abnormal FEV_1 to develop and to reach a function level associated with shortness of breath, usually an FEV_1 of about 1.2 to 1.5 liters. Thus, a smoker who is losing FEV_1 at 80 ml per year or faster is clearly a candidate for the diagnosis of clinical airflow obstruction.

Summary

The causal relationship between cigarette smoking and chronic bronchitis and emphysema has been established beyond reasonable doubt. There is good evidence that a number of other host and environmental factors may also be involved but the exact nature of the relationships is not yet understood. It is therefore not yet possible to use historical information such as total cigarette consumption, place of residence and occupation to construct a profile of the high-risk or susceptible smoker. It is clear, however, that in only a small proportion of smokers, probably fewer than 10 percent, clinical airflow obstruction develops, and in a small proportion of these the crippling form of the disease develops.

Until more is learned about the interrelation of the factors involved in COPD, the practical approach to identifying the smoker in whom clinical airflow obstruction is going to develop is to follow all smokers with spirometric tests at regular intervals (for example, annually). Those persons whose test results fall in the low normal range in early or midadult life and those who show an unexpectedly rapid decline in function should be considered to fall in the high-risk category.

REFERENCES

1. Williams LLB: Middle Age and Old Age. London, Oxford University Press, 1925
2. The Health Consequences of Smoking, 1975. US National Clearinghouse for Smoking and Health, DHEW Publication No. (CDC) 76-8704. US Department of Health, Education, and Welfare, 1976
3. The Health Consequences of Smoking, A Reference Edition. US National Clearinghouse for Smoking and Health. US Department of Health, Education, and Welfare, 1976
4. Higgins ITT: Epidemiology of Chronic Respiratory Disease: A Longitudinal Review, EPA Report No. 650/1-74-007. National Technical Information Service, US Department of Commerce, Springfield VA, 1974
5. American Thoracic Society: Definitions and classification of chronic bronchitis, asthma, and pulmonary emphysema. Am Rev Resp Dis 85:762-768, May 1962
6. Thurlbeck WM: Chronic Airflow Obstruction in Lung Disease. Philadelphia, WB Saunders Co., 1976
7. Macklem PT: Obstruction in small airways—A challenge to medicine. Am J Med 52:721-724, Jun 1972
8. Fletcher B, Peto R, Tinker C, et al: The Natural History of Chronic Bronchitis and Emphysema. New York, Oxford University Press, 1976
9. Bates DV: The fate of the chronic bronchitic: A report of the ten-year follow-up in the Canadian Department of Veterans' Affairs Coordinated Study of Chronic Bronchitis. Am Rev Resp Dis 108:1043, Nov 1973
10. Ruysh F: Observationes Anatomico—Chirurgicae, *In* Tractatio Anatomica, Vol. 1. Amsterdam, 1721, cited in Thurlbeck, 1976, Ref 6
11. Sydenham T: The Whole Works of that Excellent Physician, Dr. Thomas Sydenham: Wherein Not Only the History and Cures of Acute Diseases are Treated of, after a New and Accurate Method; but also the Shortest and Safest Way of Curing Most Chronic Diseases, 7th Ed, Pechey J (trans). London, M. Wellington, 1917, cited in Thurlbeck, 1976, Ref 6
12. Jackson J Jr, cited by Osler W: The Principles and Practice of Medicine, 6th Ed. New York, D. Appleton Co, 1905, p 634
13. Osler W: The Principles and Practice of Medicine, 6th Ed. New York, D. Appleton Co, 1905
14. Hurst A: Familial emphysema. Am Rev Resp Dis 80 (suppl): 179-180, Jul 1959
15. Wimpfheimer F, Schneider L: Familial emphysema. Am Rev Resp Dis 83:697-703, May 1961
16. Hole BV, Wasserman K: Familial emphysema. Ann Intern Med 63:1009-1017, Dec 1965
17. Larson RK, Barman ML: The familial occurrence of chronic obstructive pulmonary disease. Ann Intern Med 63:1001-1007, Dec 1965
18. Cederlof R, Friberg L, Jonsson E, et al: Morbidity among monozygotic twins. Arch Environ Health 10:346-350, Feb 1965
19. Higgins M, Keller J: Familial occurrence of chronic respiratory disease and familial resemblance in ventilatory capacity. J Chron Dis 28:239-251, Apr 1975
20. Cohen BH, Ball WC Jr, Bias WB, et al: A genetic-epidemiologic study of chronic obstructive pulmonary disease. Johns Hopkins Med J 137:95-104, Sep 1975
21. Cohen BH, Ball WC Jr, Brashears S, et al: Risk factors in chronic obstructive pulmonary disease (COPD). Am J Epidemiol 105:223-232, 1977
22. Schilling RSF, Letai AD, Hui SL, et al: Lung function, respiratory disease, and smoking in families. Am J Epidemiol 106:274-283, 1977
23. Laurell CB, Eriksson S: The electrophoretic α_1-globulin pattern of serum in α_1-antitrypsin deficiency. Scan J Clin Lab Invest 1:132-140, 1963

24. Kueppers F, Black LF: α_1-Antitrypsin and its deficiency. Am Rev Resp Dis 110:176-194, Aug 1974

25. Morse JO: Alpha$_1$-antitrypsin deficiency (I). N Engl J Med 299:1045-1048, Nov 9, 1978

26. Morse JO: Alpha$_1$-antitrypsin deficiency (II). N Engl J Med 299:1099-1105, Nov 16, 1978

27. Mendelssohn: The Journal of the Russian National Health Society, Sep 1897, cited in Lancet 2:952-953, 1897

28. Brown RG, McKeown T, Whitfield AGW: A note on the association between smoking and disease in men in the seventh decade. Br J Prev Soc Med 11:162-164, Apr 1957

29. Greene BA, Berkowitz S: Tobacco bronchitis: An anaesthesiologic study. Ann Intern Med 40:729-742, Apr 1954

30. Higgins ITT: Respiratory symptoms, bronchitis, and ventilatory capacity in random sample of an agricultural community. Br Med J 2:1198-1203, Nov 23, 1957

31. Higgins ITT, Cochran JB: Respiratory symptoms, bronchitis, and disability in a random sample of an agricultural population. Tubercle 39:296-301, 1958

32. Higgins ITT, Oldham PD, Cochrane AL, et al: Respiratory symptoms and pulmonary disability in an industrial town: Survey of a random sample of the population. Br Med J 2:904, Oct 20, 1956

33. Palmer KNV: The role of smoking in bronchitis. Br Med J 1:1473-1474, Jun 26, 1956

34. Payne M, Kjelsberg M: Respiratory symptoms, lung function, and smoking habits in an adult population. Am J Pub Health 54: 261-277, Feb 1964

35. Lowell FC, Franklin W, Michelson AL, et al: Chronic obstructive pulmonary emphysema: A disease of smokers. Ann Intern Med 45:268-274, Aug 1956

36. Flick AL, Paton RR: Obstructive emphysema in cigarette smokers. Arch Intern Med 104:518-526, 1959

37. Whitfield AGW Arnott WM, Waterhouse JAH: The effect of tobacco on lung-volume. Q J Med 20:141-147, 1951

38. Franklin W: The effect of smoking on pulmonary function in a working adult population. J Clin Invest 37:895, Jun 1958

39. Higgins ITT: Tobacco smoking, respiratory symptoms, and ventilatory capacity. Br Med J 1:325-329, Feb 7, 1959

40. Edelman NH, Mittman C, Norris AH, et al: The effects of cigarette smoking upon spirometric performance of community dwelling men. Am Rev Resp Dis 94:421-429, Sep 1966

41. Read J, Selby T: Tobacco smoking and ventilatory function of the lungs. Br Med J 2:1104-1108, Oct 28, 1961

42. Zwi S, Goldman HI, Levin A: Cigarette smoking and pulmonary function in healthy young adults. Am Rev Resp Dis 89: 73-81, Jan 1964

43. Olsen HC, Gilson JC: Respiratory symptoms, bronchitis, band ventilatory capacity in men—An Anglo-Danish comparison, with special reference to differences in smoking habits. Br Med J 1:450-456, Feb 13, 1960

44. Comroe JH, Fowler WS: Lung function studies—VI. Detection of uneven alveolar ventilation during a single breath of oxygen. Am J Med 10:408-413, Apr 1951

45. McCarthy DS, Spencer R, Greene R, et al: Measurement of 'closing volume' as a simple and sensitive test for early detection of small airway disease. Am J Med 52:747-753, Jun 1972

46. Buist AS, Van Fleet DL, Ross BB: A comparison of conventional spirometric tests and the test of closing volume in an emphysema screening center. Am Rev Resp Dis 107:735-743, May 1973

47. Buist AS, Ross BB: Quantitative analysis of the alveolar plateau in the diagnosis of early airway obstruction. Am Rev Resp Dis 108:1078-1087, Nov 1973

48. Knudson RJ, Lebowitz MD, Burton AP, et al: The closing volume test: Evaluation of nitrogen and bolus methods in a random population. Am Rev Resp Dis 115:423-434, Mar 1977

49. Buist AS, Ghezzo H, Anthonisen NR, et al: Relationship between the single breath N_2 test and age, sex, and smoking habit in three North American cities. Am Reu Resp Dis 120:(In press) Aug 1979

50. Ashley F, Kannel WB, Sorlie PD, et al: Pulmonary function: Relation to aging, cigarette habit, and mortality. Ann Intern Med 82:739-745, Jun 1975

51. Higgins ITT, Oldham PD: Ventilatory capacity in miners—A five-year follow-up study. Br J Indus Med 19:65, Jan 1962

52. Fletcher B, Peto R, Tinker C, et al: The Natural History of Chronic Bronchitis and Emphysema. New York, Oxford University Press, 1976

53. Ferris BG, Higgins ITT, Higgins MW, et al: Chronic nonspecific respiratory disease in Berlin, New Hampshire, 1961 to 1967—A follow-up study. Am Rev Resp Dis 107:110, Jan 1973

54. Petty TL, Pierson DJ, Dick NP, et al: Follow-up evaluation of a prevalence study for chronic bronchitis and chronic airway obstruction. Am Rev Resp Dis 114:881, Nov 1976

55. Morris JF, Koski WA, Johnson LC: Spirometric standards for healthy nonsmoking adults. Am Rev Resp Dis 103:57, Jan 1971

56. Ferris BG, Anderson DO, Zickmantel R: Prediction values for screening tests of pulmonary function. Am Rev Resp Dis 91: 252, Feb 1965

57. Higgins MW, Keller JB: Seven measures of ventilatory lung function. Am Rev Resp Dis 108:258, Aug 1973

58. Dickman ML, Schmidt CD, Gardner RM, et al: On-line computerized spirometry in 783 normal adults. Am Rev Resp Dis 100:780, Dec 1969

59. Buist AS, Nagy J: A longitudinal study of smokers and nonsmokers: Five to six year follow-up using spirometry and the single breath N_2 test, *In* Petty TL, Zwillich C (Eds): Proc 22nd Aspen Lung Conference, June 13-16, 1979, Chest(Suppl):1979

60. Burrows B, Knudson RJ, Cline MG, et al: Quantitative relationships between cigarette smoking and ventilatory function. Am Res Resp Dis 115:195-205, Feb 1977

61. Kuperman AS, Riker JB: The variable effect of smoking on pulmonary function. Chest 63:655-660, May 1973

62. Mueller RE, Keble DL, Plummer J, et al: The prevalence of chronic bronchitis, chronic airway obstruction and respiratory symptoms in a Colorado city. Am Rev Resp Dis 103:209-228, Feb 1971

63. Kass I, O'Brien LE, Zamel N, et al: Lack of correlation between clinical background and pulmonary function tests in patients with chronic obstructive pulmonary disease. Am Rev Resp Dis 107:64-69, Jan 1973

64. Holland WW, Halil T, Bennett AE, et al: Factors influencing the onset of chronic respiratory disease. Br Med J 2:205-208, Apr 26, 1969

65. Reid DD, Fairbairn AS: The natural history of chronic bronchitis. Lancet 1:1147-1152, May 31, 1958

66. Rosenbaum S: Home localities of national servicemen with respiratory disease. Br J Prev Soc Med 15:61-67, Apr 1961

67. Colley JRT, Reid DD: Urban and social origins of childhood bronchitis in England and Wales. Br Med J 32:213-217, Apr 25, 1970

68. Colley JRT, Douglas JWB, Reid DD: Respiratory disease in young adults: Influence of early childhood lower respiratory tract illness, social class, air pollution and smoking. Br Med J 3:195-198, Jul 28, 1973

69. Burrows B, Lebowitz MD, Knudson RJ: The relationship of childhood respiratory illness to adult obstructive airway disease. Am Rev Resp Dis 115:751-760, May 1977

70. Lebowitz MD, Burrows B: The relationship of acute respiratory illness history and the prevalence and incidence of obstructive lung disorders. Am J Epidemiol 105:544, 1977

71. Rooney JC, Williams HE: The relationship between proved viral bronchiolitis and subsequent wheezing. J Pediatr 79:744-747, Nov 1971

72. Melia RJW, Florey CduV, Altman DG, et al: Association between gas cooking and respiratory disease in children. Br Med J 2:149-152, Jul 16, 1977

73. Logan WPD: Mortality in the London fog incident, 1952. Lancet 1:336-338, Feb 14, 1953

74. Greenburg L, Field F, Reed JI, et al: Air pollution and morbidity in New York City. JAMA 182:161, 1962

75. Schrenk HH, Heimann H, Clayton CD, et al: Air polluition in Donora, Pennsylvania. Pub Health Bull 306, 1949

76. Firket J: The cause of the symptoms found in the Meuse Valley during the fog of December, 1930. Bull Roy Acad Med Belgium 11:683-739, 1931

77. Reid DD: Air pollution as a cause of chronic bronchitis. Proc Roy Soc Med 57:965-968, Oct 1964

78. Douglas JWB, Waller RE: Air pollution and respiratory infection in children. Br J Prev Soc Med 20:1-8, Jan 1966

79. ATS Ad Hoc Committee: Health Effects of Air Pollution. Presented at ATS Scientific Assembly on Occupational and Environmental Health. New York, American Thoracic Society, 1978

80. Greenhow EH: Report of the M. O. of the Privy Council, Third Report, London, Her Majesty's Stationery Office 1860

81. Copland J: The Forms, Complications, Causes, Prevention and Treatment of Consumption and Bronchitis, Comprising also the Causes and Prevention of Scrofule. London, Longmans and Green and Co, 1866

82. Registrar General's Decennial Supplement, 1951. Her Majesty's Stationery Office, London, 1957

83. Enterline PE: Mortality rates among coal miners. Am J Pub Health 54:758-768, May 1964

84. Brinkman GL, Block DL, Cress C: Effects of bronchitis and occupation on pulmonary ventilation over an 11-year period. J Occup Med 14:615-620, 1972

85. Kauffmann F, Brille D, Lellough J: Factors related to FEV_1 slope between two cross-sectional surveys 1960-1972. Scand J Resp Dis 57:313-314, 1976

86. Bouhuys A, Van deWoestijne KP: Respiratory mechanics and dust exposure in byssinosis. J Clin Invest 49:106-118, Jan 1970

87. Molyneux MKB, Tombleson JBL: An epidemiological study of respiratory symptoms in Lancashire mills, 1963-1966. Br J Indust Med 27:225-234, Jul 1970

88. Schraj PE, Gullett AD: Byssinosis in cotton textile mills. Am Rev Resp Dis 101:497-503, Apr 1970

89. Bouhuys A, Wolfson RL, Horner DW, et al: Byssinosis in cotton textile workers—Respiratory survey of a mill with rapid labor turnover. Ann Intern Med 71:251-269, Aug 1969

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Pulmonary Aspiration

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *In this conference we will discuss pulmonary aspiration, a subject that has caused considerable controversy. Dr. John Little from the Chest Service at the San Francisco General Hospital will present this topic.*

DR. LITTLE:† The title "Pulmonary Aspiration" has been carefully chosen and the term aspiration pneumonia has been deliberately avoided because of the confusion surrounding it. Aspiration pneumonia has been used elsewhere to denote both the syndrome of aerobic-anaerobic pulmonary infection secondary to aspiration of normal oral flora as well as the chemical pneumonitis and respiratory distress that follow aspiration of gastric acid—two distinct disease processes with differing pathophysiology and treatment (Table 1). Given the widespread use of this imprecise term, it is not surprising that muddled thinking and inconsistent practices accompany its use.

Dorland's Medical Dictionary defines aspiration pneumonia as "pulmonary inflammation caused by inhaled material which is inherently toxic or which initiates a toxic response." Many substances satisfy this definition, a point that Bartlett and Gorbach[1] made clear in a review outlining the triple threat of aspiration (Table 2). The pathophysiology of the disease processes induced by toxic fluids, bacterial pathogens and inert substances, and their subsequent management, are so diverse that it is not adequate to speak of an aspiration pneumonia with its implied unitary concept of disease. Furthermore, the word pneumonia has such strong connotations of infection that its use makes it virtually impossible to resist writing an order for penicillin. For more precise evaluation and logical management, we should discard the term aspiration pneumonia in favor of "pulmonary aspiration of . . .." Today we will focus on the syndrome of gastric acid aspiration and its relationship to bacterial infection, and begin by examining the process of aspiration.

Gastric Acid Aspiration

The frequent occurrence of aspiration of *oral* contents into the lungs is well documented. It has been studied in a variety of patients including those who have had surgical operations and tracheotomines. In a recent study Huxley and coworkers reexamined the frequency of aspiration of oral contents during sleep using a radioisotope-labeled liquid instilled into the nasopharynx.[2] In a group of patients with depressed consciousness, lung scans done the next morning showed isotopes in the lungs of 70 percent; this high value is not unexpected and similar results have been reported before. More surprising, however, was the finding

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TABLE 1.—*Aspiration Syndromes*

	Gastric Acid	*Community-Acquired Mixed Aerobic-Anaerobic Pneumonia*
Pathogenesis	Chemical burn	Bacterial infection
Event	Overt or occult	Occult
Onset	Acute	Gradual
Syndrome	Respiratory distress Hypoxia	Indolent febrile illness
Examination findings	Diffuse rales	Localized
Chest x-ray findings	Patchy alveolar	Localized infiltrate Abscess
Gram stain	Leukocytes No/scant organisms	Leukocytes Abundant, mixed organisms
Therapy	Oxygen Ventilatory support	Penicillin
Course	(1) Rapid death (2) Stabilization at 24 to 36 hours then, either progressive recovery or late bacterial pneumonia	Benign, perhaps protracted

that there were positive scans in 45 percent of normal subjects studied on only one occasion, and that in an additional 25 percent there was evidence of possible aspiration. These results suggest that nearly everyone aspirates oral contents at some time during sleep. The relatively infrequent occurrence of bacterial pneumonia in normal hosts and the increased incidence of these pneumonias associated with structural lung disease, alcoholism and viral infections suggest (1) that the normal host defenses of the lung—the mucociliary apparatus, alveolar macrophage and immunologic mechanisms—are generally able to clear aspirated bacteria and (2) that dysfunction of this system results in an increased incidence of infection.

In contrast to oral contents, aspiration of *gastric* contents occurs much less frequently, although gastric aspiration is the leading cause of death associated with anesthesia. Dye instilled in the stomachs of preoperative patients can be found in tracheal secretions intraoperatively in 10 percent to 15 percent of the cases studied. In ambulatory postoperative patients studied by instillation of barium into the stomach before sleep, x-ray studies of the chest showed evidence of pulmonary aspiration in less than 2 percent. Accurate data on the incidence of gastric aspiration in other circumstances are lacking. The point is often made that because gastric aspiration is frequently an occult event and difficult to document unless witnessed, it is underdiagnosed. In contrast to aspiration of oral contents, the potentially deadly nature of gastric aspiration is underscored by a quoted mortality of 10 percent to 70 percent.

TABLE 2.—*Classification of Substances That May Induce Aspiration Syndromes*

Toxic Fluids	
Acid	Bile
Hydrocarbons	Alcohol
Mineral oil	Animal fats
Bacterial Pathogens	
Inert Substances	
Saline	Particulate matter

Given the occult nature of gastric aspiration, its diagnosis often depends on a high index of suspicion based on an awareness of the circumstance in which it occurs (Table 3). Two major factors predispose to significant gastric aspiration: (1) Alterations in consciousness or the gag reflex as found during overdose of alcohol, general anesthesia, debilitating illness, sedation or drug abuse, and convulsive disorders and (2) an alteration in normal swallowing and esophageal function induced by organic disease as well as iatrogenic intervention.

Pathophysiology

The severity of dysfunction following gastric aspiration is determined by the volume and acidity of the aspirate. Introduction of a small volume into a small part of the lung will cause minimal physiologic dysfunction. Yet, whole lungs may be lavaged by saline during bronchoscopy with only a small and transient fall in arterial oxygen

TABLE 3.—*Predisposing Factors to Gastric Aspiration*

Impaired Consciousness
General anesthesia
Severe illness or obtundation
Drug abuse
Convulsive disorders
Trauma
Esophageal and Swallowing Disorders
Nasogastric tube
Tracheotomy
Esophageal sphincter incompetence
Achalasia
Obstruction

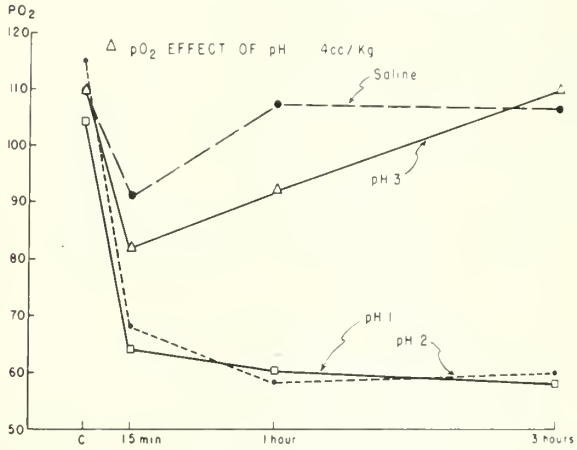

Figure 1.—Effect of pH of aspirated fluid on PaO_2 in four animals. (Reproduced with permission from Awe et al.[3])

tension (Pa_{O_2}) and abnormalities of lung mechanics resulting. More important, the acidity of the aspirate is the primary determinant of lung injury. Several studies have indicated that instillation of solutions with a pH higher than 2.5 produce minimal changes in gas exchange, lung mechanics and histology—alterations which are similar in extent and duration to those produced by equal volumes of saline.[3] In contrast, instillation of solutions with a pH lower than 2.5 produces characteristic abnormalities in these measurements (Figure 1). Other contents of gastric juice, including gastric enzymes, apparently do not contribute to lung damage. When gastric juice is boiled to remove gastric enzymes and then instilled into the lungs of experimental animals, a syndrome identical to that seen following untreated gastric juice instillation occurs. Conversely, when the acidity of gastric juice is neutralized but its enzyme content is left unchanged, no lung damage occurs following instillation. How do these data relate to man? The pH of gastric contents in fasting persons generally ranges from

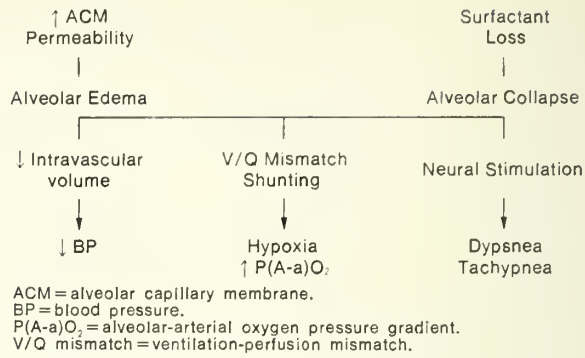

Figure 2.—Sequence of events in alveoli following gastric acid aspiration.

1.5 to 2.4, although food may buffer the acidity somewhat. However, the extent of this buffering effect may not be adequate to raise the pH above 2.5 in many persons and may be short-lived because the presence of food in the stomach stimulates the secretion of gastric acid. Therefore, the finding of food particles in the airway in no way ensures that aspirated gastric acid has been adequately buffered to minimize lung injury.

The pathophysiology of gastric aspiration is initiated as the gastric acid enters the lung. A chemical burn from the central airways to the alveoli occurs within five seconds of aspiration. Within 15 seconds, virtually all of the acid has been effectively neutralized, but by this time damage has been done to both airways and gas exchange units. Surfactant lining of the alveolar surface is destroyed with a consequent increase in surface tension and a tendency to alveolar collapse (Figure 2). Within minutes, gross atelectasis may be evident. The normally impermeable alveolar epithelium loses its integrity and plasma leaks from the interstitial into the alveolar spaces. If the extravasation of intravascular volume into the lung is sufficient, hypotension and shock may occur. Stimulation of interstitial neural receptors produces the sense of dyspnea and tachypnea. Increased extravascular lung water produces a noncompliant or stiff lung with decreased lung volumes, ventilation-perfusion mismatching with resultant hypoxia and a widened alveolar-arterial oxygen gradient. You will remember that of the three most common causes of hypoxia—hypoventilation, ventilation-perfusion mismatching and right-to-left shunting—only hypoventilation is associated with a normal alveolar-arterial oxygen gradient of less than 15 mm of mercury.

Following gastric aspiration, the fall in arterial Po_2 begins immediately and may be severe within

Fluid exudation —— V/Q mismatch → Hypoxia
↑ P(A-a)O_2

Constriction → Dyspnea
Wheezing

Tissue injury → Fever

Destruction of mucociliary system → Decreased clearance inhaled/aspirated materials

P(A-a)O_2 = alveolar-arterial oxygen pressure gradient.
V/Q mismatch = ventilation-perfusion mismatch.

Figure 3.—Sequence of events in airways following gastric acid aspiration.

TABLE 4.—*Clinical Signs After Aspiration of Gastric Contents**

Clinical Signs	*Number*	*Percent*
Latent period		
0 to one hour	48	96
Two hours	2	4
Fever, total	47	94
37.2 to 38.9°C (99 to 102°F)	24	48
>38.9°C (>102°F)	23	46
Tachypnea	39	78
Rales	36	72
Cough	18	36
Cyanosis	16	32
Wheezing	16	32
Apnea	15	30
Shock	12	24

*Reproduced with permission from Bynum and Pierce[4]

minutes. Bynum and Pierce observed that arterial blood specimens drawn immediately after witnessed gastric aspirations showed a mean alveolar-arterial oxygen difference of 120 mm of mercury in patients breathing supplemental oxygen, signifying a severe gas exchange abnormality.[4] This combination of hypoxia and an increased alveolar-arterial gradient is invariably the first sign of aspiration, preceding radiographic changes by several hours. In the airways (Figure 3), fluid exudation impairs normal distribution of ventilation, thereby contributing further to hypoxia. Reflex responses may trigger bronchoconstriction with dyspnea and, on occasion, wheezing. Massive tissue injury is followed by fever, whereas destruction of the ciliated epithelium inactivates one of the primary defense mechanisms of the lung and predisposes the patient to subsequent bacterial pulmonary infection.

Clinical Presentation

The clinical presentation of gastric aspiration has been well described (Table 4). Two salient points are illustrated in Table 4: First, in almost all cases, physiologic dysfunction associated with

Figure 4.—Roentgenogram of chest following gastric aspiration showing the absence of the left diaphragmatic shadow indicating left lower lobe collapse.

acid aspiration develops within minutes and, second, this fulminant process may be clinically subtle. The most common manifestations—hypoxia, tachypnea, fever and rales—may be easily overlooked in patients who frequently are obtunded or unconscious. The more obvious clinical signs such as cough, cyanosis and wheezing occur approximately a third of the time. Consequently, respiratory failure may persist undetected until more dramatic events precipitate its discovery. The development of abnormalities that can be noted on chest x-ray films lags behind these initial changes by several hours. The infiltrates tend to be described as patchy and fluffy or alveolar. Their distribution depends on the patient's position at the time of aspiration and on the anatomy of the airway. Because the right main bronchus is more nearly a straight tube and consequently favors entry of liquid, the right lung is more frequently involved than the left. Because patients are usually supine at the time of aspiration, liquid tends to flow into the posterior segmental orifices, such as the superior or posterior segments of the right lower lobe. However, it should be emphasized that the process may involve any lobe. Other complications may include segmental or lobar collapse. In Figure 4, the left lower lobe collapse is indicated by the absence of the left diaphragmatic shadow and the shift of the mediastinum to the left. Pleural or cavitary changes are unusual. The extent of radiographic changes does not correlate with the severity of hypoxia, especially in its early stages. Abnormal-

ities shown on x-ray films may progress for 24 to 36 hours but then stabilize or begin to improve. Subsequent worsening indicates the presence of complications that require an explanation; repeated aspiration, pulmonary edema from widespread pulmonary capillary permeability or bacterial infection must be considered.

Because of its occult nature, there is no simple and reliable means of diagnosing acid aspiration. Because of the rapidity with which acid is neutralized in the lung, determination of the pH of tracheal secretions is useless. Finding food particles in the airway or the presence of hemorrhagic tracheobronchitis on fiberoptic bronchoscopy is highly suggestive. However, there is no sure means of confirming the suspected diagnosis.

Therapy

Therapy follows logically from the pathophysiology of this disorder. Hypoxemia should be remedied by supplemental oxygen. If alveolar edema and collapse produce sufficiently severe shunting of mixed venous blood, systemic oxygen transport may not be adequately maintained by administration of oxygen using a mask. In this event, intubation and mechanical ventilation may be required. Positive end-expiratory pressure (PEEP) is widely used in the management of the adult respiratory distress syndrome. By holding airway pressure at positive values, new groups of alveoli are opened and ventilated, and gas exchange is improved through better matching of ventilation and perfusion.

Widespread use of PEEP, however, has also shown that not all of its effects are beneficial. A fall in cardiac output may accompany the use of PEEP, although the mechanism or mechanisms responsible remain under debate. Those most frequently cited are a right ventricular decrease in preload due to a reduction in venous return, a decrease in myocardial contractility or a decrease in left ventricular compliance. In patients with gastric aspiration, mechanical ventilation and PEEP have been associated with a significantly higher incidence of pneumothorax. Finally, there are data suggesting that sequential increases in PEEP may improve oxygenation while concurrently increasing fluid movement into lung parenchyma. Thus, improved gas exchange may, in some instances, be accompanied by further lung injury. Therefore, PEEP should supplement mechanical ventilation when adequate oxygen transport can be maintained only with excessive inspired oxygen concentrations. That is, PEEP should be added if a patient with an appropriate cardiac output, indicated by an arterial-mixed venous oxygen content difference of 5 volumes per dl or less, cannot maintain an arterial Po_2 greater than or equal to 60 mm of mercury with an inspired oxygen content of less than 50 percent.

Persistent hypotension reflects a decreased intravascular volume following loss of fluid into the lung. Fluid management must strike a balance between an intravascular volume adequate to perfuse vital organs and the tendency for further fluid extravasation into the lung at normal intravascular pressures. In the normal lung, increases in pulmonary capillary hydrostatic pressure up to 20 to 25 mm of mercury can occur before a large accumulation of fluid occurs. However, if the permeability of the alveolar capillary membrane is increased, transudation of fluid will occur at significantly lower pressures. In patients with serious involvement, pulmonary capillary hydrostatic pressure should be monitored by placement of a flow-directed pulmonary artery catheter. A rule of thumb for fluid management is that the pulmonary capillary wedge pressure should be kept as low as is consistent with adequate cardiac output and renal function.

Fever is not treated with antipyretics unless physiologic complications, such as angina or cardiac failure, are precipitated by increased metabolic demands.

The use of corticosteroids following gastric aspiration is controversial. In theory, corticosteroids may be of benefit in decreasing the inflammatory response following injury and in preventing platelet and leukocyte aggregation with subsequent thrombosis of the pulmonary microvasculature. But various experimental and clinical studies designed to evaluate the efficacy of steroids in gastric aspiration have produced conflicting conclusions. A definitive double-blind, randomized study remains to be done. Bynum and Pierce[4] studied this problem in a retrospective analysis (Table 5). Although statistically significant differences could not be shown, the use of corticosteroids following gastric aspiration was associated with a pronounced trend toward subsequent increased hospital-acquired pneumonia and mortality. The results of a prospective study by Wolfe and co-workers documented a significant incidence of Gram-negative pneumonia in patients receiving corticosteroids following gastric aspiration.[5] This finding was not surprising, given data

TABLE 5.—*Mortality and Pneumonia Incidence Following Gastric Acid Aspiration in Patients Treated and Not Treated With Corticosteroids*

	Treated No./Total (Percent)		*Untreated No./Total (Percent)*		*Test for Significance*
Mortality					
Bynum and Pierce[1]	12/33	(36)	2/17	(12)	NS
Wolfe et al[2]	8/25	(32)	5/18	(28)	NS
Subsequent Pneumonia					
Bynum and Pierce	10/33	(30)	3/17	(18)	NS
Wolfe et al	7/20	(35)	0/13	(0)	$P<0.05$

NS = not significant

TABLE 6.—*The Effects of Corticosteroids on Leukocyte Function*

Low Dose:* Kinetics	
Granulocytes:	Marrow mobilization→↑ numbers ↓ Vascular adherance→↓ Migration
Mononuclear cells:	Extracirculatory sequestration→ ↓ numbers ↓ Chemotactic response→ ↓ Migration
Dose Related: Function	
Granulocytes:	None in usual pharmacologic range
Mononuclear cells:	↓ Cellular killing ↓ Mediator production and cell interactions ↓ Immunoglobulin production

*Low dose = 20 mg of prednisone or less per day or equivalent
↑ = increased ↓ = decreased → = results in

indicating that steroid therapy may enhance oral bacterial colonization with potential pathogens.[6]

This group of patients is, by definition, at risk for further aspiration of oral secretions and, after acid-induced injury to the ciliated epithelium, compromised in its ability to clear aspirated organisms. This depression of local host defenses may be aggravated by corticosteroid use. As shown in Table 6, the high doses of corticosteroids generally used in treating this condition suppress both granulocyte kinetics as well as mononuclear cell kinetics and function. In summary, corticosteroids in gastric acid aspiration appear to have no effect on the injury but do depress host defenses and predispose to subsequent bacterial pulmonary infection. Given these findings, corticosteroids should not be used in gastric aspiration.

Gastric Acid Aspiration and Bacterial Pneumonia

The relationship between gastric acid aspiration and bacterial pneumonia, and the proper use of antibiotics in these circumstances, should be clarified. The course following a single aspiration episode may be (1) rapid death, generally within the first 24 hours, (2) stabilization of the physiologic dysfunction and radiographic progression within 24 to 36 hours, followed by an uneventful recovery or (3) the development of a late, generally aerobic bacterial pneumonia.

Bacterial pulmonary infection may occur in 20 percent to 45 percent of patients following gastric acid aspiration. Moreover, bacterial pneumonia is the leading cause of death in those patients who survive the initial event. Mechanisms that may induce bacterial pneumonia include inhalation of aerosolized organisms, hematogenous spread, direct extension from a contiguous site and aspiration of oropharyngeal secretions. However, in the setting of gastric aspiration, virtually all pneumonias occur by aspiration of oropharyngeal secretions. Three conditions after gastric acid aspiration render patients at great risk for pneumonia: (1) the predisposition to repeat aspiration of oropharyngeal secretions, (2) the gastric acid-induced injury to the mucociliary apparatus and (3) the possibility that subsequently aspirated oropharyngeal secretions will contain pathogenic organisms.

The organisms that cause pneumonia following gastric aspiration in patients in hospital or subsequently admitted to hospital are frequently Gram-negative enteric bacilli and Staphylococcus aureus. This is true of nosocomial pneumonias as a group and is in distinct contrast to the bacteriology of community-acquired pneumonias. Many pneumonias which follow gastric aspirations by persons in the community who are subsequently admitted to hospital seem to conform to this nosocomial pattern because bacterial pneumonia is rarely an immediate complication following acid aspiration.[1,7] Instead, bacterial pneumonia is a secondary event, occurring in patients in one study within a range of two to ten days after aspiration and in most of these patients within

TABLE 7.—*Frequency of Gram-Negative Bacillary Presence and Predominance in Sputum of Controls, Hospital-Associated Persons, and Inpatients*

	Frequency of Gram-Negative Organisms (Percent)	*Predominant Aerobic Organisms*
Normal Subjects		
Nonhospital-associated	2	α streptococci
Hospital-associated ..	2	Streptococcus pneumoniae
Adults Admitted to Hospital		
Psychiatric patients ..	2	Streptococcus pneumoniae
Moderately ill	30	Streptococcus pneumoniae
ICU Patients		
Within 24 hours	22	50% to 70% Gram negative
Within 72 hours	40	50% to 70% Gram negative
Moribund	>70	50% to 70% Gram negative

ICU = Intensive Care Unit

three to five days.[4] The reasons for this pattern are not clear but may be related to the degree of acidity of the aspirate. The pH of 2.5 or less required to produce lung damage and subsequent predisposition to infection will also destroy both aerobic and anaerobic organisms.[8] Thus, aspiration of gastric juice sufficiently acid to damage the lung will be virtually sterile.

It is likely that oropharyngeal secretions enter the lung concurrently with gastric juice. The rarity of bacterial pneumonia in the immediate post-aspiration period may be the result of bacteria entering in concentrations too small to produce infection, the dilution of aspirated bacteria by gastric acid into similarly small inocula or the destruction of the bacteria by gastric acid. In sum, these patients do not become infected coincident with gastric aspiration, but several days later. In the meantime they are admitted to hospital and a change in oropharyngeal flora occurs which is primarily determined by two factors. The first is the severity of illness of the host. In two studies, Johanson and co-workers[9-10] observed that exposure to the hospital setting per se has no effect on oropharyngeal colonization with Gram-negative enteric organisms (Table 7). Instead, they found that the sicker the patient, the greater was the incidence of colonization. In patients admitted to the intensive care unit from the community, more than 20 percent were colonized with Gram-negative bacilli within 24 hours, and the overall incidence of such colonization approached 50 percent within three days. In patients with primary respiratory disease such as post-gastric aspiration, this figure approached 75 percent. Furthermore, patients so colonized had a far higher incidence of pneumonia.

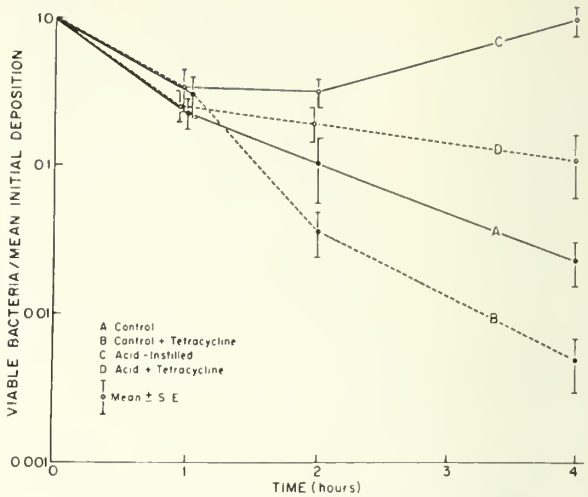

Figure 5.—Change in the ratio of remaining viable bacteria to mean initial bacterial deposition at intervals after exposure to airborne Streptococcus pneumoniae in four groups of rats. Intratracheal instillation of 0.1 normal solution of hydrochloric acid, 4.0 ml per kg of body weight, was performed four hours before aerosol exposure. Tetracycline, 30 mg per kg of body weight, was administered intraperitoneally at the same time. (Reproduced with permission from Johanson WG et al.[12])

The second factor producing a change in oropharyngeal flora is the use of antibiotic drugs. The normal flora, particularly Streptococcus viridans, inhibits the growth of many Gram-negative bacilli and staphylococci *in vitro*. Attempts to induce colonization in normal subjects by aerosol or bolus inoculation with Gram-negative organisms have not been successful. Furthermore, Sprunt has shown that the persistence of this normal flora in the hospital setting is apparently effective in inhibiting subsequent colonization with Gram-negative organisms.[11] The eradication of Streptococcus viridans by antibiotics administered intraoperatively in patients undergoing elective cardiac valve replacement was associated with a significantly higher rate of Gram-negative colonization compared with those patients in whom the organism persisted. This association between antibiotic use and colonization has also been observed by Johanson and co-workers.[9]

Not only does the potentially infecting flora change, but host defenses are breached. Acid aspiration denudes the airway and destroys the mucociliary apparatus that clears aspirated bacteria. Lung clearance of bacteria has been examined in an acid aspiration model (Figure 5). In comparison to normal animals, acid-damaged

animals (curve C) have substantially diminished clearance of instilled bacteria,[12] and the use of an appropriate antibiotic is significantly less effective in clearing bacteria from the acid-damaged lung (curve D).

Should antibiotic drugs be used after gastric aspiration in patients who are at high risk for bacterial pneumonia to develop? A widespread and virtual reflex response is to use variable doses of penicillin or more potent antibiotics. However, given that pneumonia is rarely an initial complication of gastric aspiration, this practice amounts to an attempt at prophylaxis that is both ineffective and potentially harmful. Since the discovery of antibiotic drugs, many attempts have been made to prevent pneumonia in patients at risk by sterilizing the oropharynx. Ultimately, all of these attempts have failed because of (1) the ultimate inability to sterilize the oropharynx, (2) the replacement of the original flora with one inherently more dangerous or (3) the emergence of drug-resistant organisms. In patients who have suffered gastric aspiration, the administration of antibiotics has resulted in either little effect[4] or a high incidence of pneumonia.[13]

A reasonable approach to the management of patients following gastric aspiration is to anticipate the development of bacterial pneumonia several days after the primary event, and to use antibiotic drugs only when infection is documented. Gram stain of pulmonary secretions immediately following gastric aspiration generally shows polymorphonuclear cells in response to the acid burn and a meager or mixed bacterial flora. Interim monitoring requires *staging* the sputum with a daily Gram stain examination for quantitative and qualitative assessment of leukocytes and bacteria, and periodic cultures for identification and antimicrobial sensitivity testing of the predominant organisms. Sputum culturing provides a basis for sound antibiotic choice if infection occurs, but not a means of diagnosing infection. This diagnosis relies on clinical, not bacteriologic events. The differentiation between colonization with pathogenic organisms, almost universal in this circumstance, and infection is made by a composite evaluation of several clinical features: (1) a new or heightened fever, (2) a new or increased radiographic infiltrate appearing 36 to 48 hours or longer after aspiration, (3) a peripheral leukocytosis and (4) an increased sputum purulence with, occasionally, the emergence of a predominant organism. This approach avoids the inappropriate use of antibiotics with their inherent risks while providing both a sound method of diagnosing secondary pneumonia and the bacteriologic data on which to base appropriate therapy.

In conclusion, it is apparent that appropriate management of pulmonary aspiration depends on a clear understanding of the pathophysiology associated with the aspirate. Pathologic processes induced by these events may be diverse and management must be individually determined. Aspiration of gastric acid may produce a fulminant and deadly form of pulmonary edema in which intubation, mechanical ventilation and sophisticated cardiopulmonary monitoring are required, but in which corticosteroids have no useful role. Bacterial pulmonary infection may follow gastric acid aspiration by several days, but is rarely a concurrent event. It is recommended that a subsequent infection be anticipated and the patient monitored in the interim as described above. Antibiotics should be administered only when infection is documented by appropriate changes in sputum Gram stain, fever, roentgenogram of the chest and peripheral leukocyte count.

REFERENCES

1. Bartlett JG, Gorbach SL: The triple threat of aspiration pneumonia. Chest 68:560-566, 1975
2. Huxley EJ, Vinoslav J, Gray WR, et al: Pharyngeal aspiration in normal adults and patients with depressed consciousness. Am J Med 64:564-568, 1978
3. Awe WC, Fletcher WS, Jacob SW: The pathophysiology of aspiration pneumonitis. Surgery 60:232-239, 1966
4. Bynum LJ, Pierce AK: Pulmonary aspiration of gastric contents. Am Rev Resp Dis 114:1129-1136, 1976
5. Wolfe JE, Bonc RC, Ruth WE: Effects of corticosteroids in the treatment of patients with gastric aspiration. Am J Med 63: 719-722, 1977
6. Kass EK, Finland M: Corticosteroids and infection. Adv Intern Med 9:45-80, 1958
7. Wynne JW, Modell JH: Respiratory aspiration of stomach contents. Ann Intern Med 87:466-474, 1977
8. Gianella RA, Broitman SA, Zancheck N: Gastric acid barrier to ingested microorganisms in man. Gut 13:251-256, 1972
9. Johanson WG, Pierce AK, Sanford JP, et al: Changing pharyngeal bacterial flora of hospitalized patients. N Engl J Med 281:1137-1140, 1969
10. Johanson WG, Pierce AK, Sanford JP, et al: Nosocomial respiratory infections with gram-negative bacilli—The significance of colonization of the respiratory tract. Ann Intern Med 77:701-706, 1972
11. Sprunt K, Leidy GA, Redman W: Prevention of bacterial overgrowth. J Infect Dis 123:1-10, Jan 1971
12. Johanson WG, Jay SJ, Pierce AK: Bacterial growth *in vivo*. J Clin Invest 53:1320-1325, 1974
13. Lewis RT, Burgess JH, Hampson LG: Cardiorespiratory studies in critical illness. Arch Surg 103:335-340, 1971

Important Advances in Clinical Medicine

Epitomes of Progress — Physical Medicine and Rehabilitation

The Scientific Board of the California Medical Association presents the following inventory of items of progress in physical medicine and rehabilitation. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in physical medicine and rehabilitation which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Physical Medicine and Rehabilitation of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Electromyographic Findings in Upper Motor Neuron Lesions

FROM THE ONSET of clinical electromyography in the 1940's until recently, certain electrical wave forms were considered indicative of direct damage to the lower motor neuron; either the cell body or the axon. Therefore, the presence of these waves could be relied upon to indicate the presence of a peripheral nerve lesion, even when the clinical signs of an upper motor neuron lesion hid signs of a mild lower motor neuron lesion.

In 1967 Goldkamp published his study of 116 hemiplegic patients showing that some 80 percent had electrical waves that were previously assumed to be present only with peripheral nerve lesions; despite the absence of a history of peripheral nerve injury. He concluded that transynaptic effect had caused the electrical changes found. An upper motor neuron lesion, therefore, had produced changes in the lower motor neuron.

Since that time, a preponderance of studies have found these wave forms in patients with upper motor neuron lesions. In a recent paper Taylor reviewed these studies and gave added evidence that an upper motor neuron lesion is indeed associated with the presence of these wave forms. He studied 22 patients with cervical or high thoracic cord lesions, all of whom showed these wave forms.

The above findings have been attributed to either transynaptic effects on the lower motor neuron, or to loss of a substance that stabilizes the excitability of the muscle cell membrane. The factors that are responsible for such changes are not known.

These studies bring into focus several different principles. Electromyographers must consider the effects of an upper motor neuron lesion and the date of onset. In hemiplegic persons, these wave forms tend to appear after one or two weeks and persist for some 18 weeks, but can persist for longer periods; especially in the distal hand and foot muscles.

For clinicians, it again illustrates the truism that the electrical wave forms are not pathognomic of any disorder. The ability to distinguish one wave form from another can be learned in a few weeks, but such information alone can be grossly misleading. The electromyographic examination must be carried out and interpreted by someone

who has extensive knowledge of clinical medicine with a special interest in neuromuscular disorders.

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REFERENCES

Goldkamp O: Electromyography and nerve conduction studies in 116 patients with hemiplegia. Arch Phys Med Rehabil 48:59-63, Feb 1967

Taylor RG, Kewalramani LS, Fowler WM Jr: Electromyographic findings in lower extremities of patients with high spinal cord injury. Arch Phys Med Rehabil 55:16-23, Jan 1974

Johnson EW, Penny ST, Kelley JP: Sequence of electromyographic abnormalities in stroke syndrome. Arch Phys Med Rehabil 56:468-473, Nov 1975

Scoliosis

SCOLIOSIS is the most deforming orthopedic problem confronting children. It is a potentially progressive condition affecting children during their active growth and significantly subsiding upon completion of spinal growth. Early recognition is mandatory so that treatment to prevent structural scoliosis can be carried out.

There are numerous causes of scoliosis but the idiopathic type is most prevalent (60 percent). Recent studies have indicated a familial preponderance and idiopathic scoliosis is now considered familial. Girls outnumber boys nine to one but no endocrine basis is known.

Early treatment, the application of a Milwaukee brace or its equivalent, has been effective. This is dynamic correction which incorporates an exercise program within the brace.

Surgical intervention employs internal instrumentation, the Harrington rod, which corrects most curves by 50 percent. Fusion after application of the rod requires cast immobilization for six to nine months.

Internal correction by the Dwyer method has gained credence. This requires sequential disectomy and instrumentation to correct the curve. Halo-pelvic or halo-femoral traction permits beneficial correction of curve preoperatively.

The numerous new surgical techniques are drastic surgical procedures that could be decreased or eliminated if early curves were detected by large scale pediatric screening.

RENE CAILLIET, MD

REFERENCES

Blount WP: Bracing for scoliosis, *In* Licht S (Ed): Orthotics, Etcetera—Physical Medicine, Vol 9. New Haven, Elizabeth Licht, Publisher, 1966

Blount WP, Bolinske J: Physical therapy in the nonoperative treatment of scoliosis. Phys Ther 47:919-925, Oct 1967

Cailliet R: Scoliosis, Philadelphia, F. A. Davis Co, 1975

Cowell HR, Hall JN, MacEwen GD: Genetic aspects of idiopathic scoliosis—A Nicholas Andry Award essay, 1970. Clin Orthop 86:121-131, 1972

Dwyer AF: Anterior instrumentation for scoliosis, *In* Robin GC (Ed): Scoliosis. New York, Academic Press, Inc, 1973

MacEwen GD, Cowell HR: Familial incidence of idiopathic scoliosis and its implication on patient treatment. J Bone Joint Surg (Am.) 92:405, 1970

Sex and Patients With Spinal Cord Injuries

SEXUAL FUNCTION, once thought to be lost after spinal cord injury, is now known to continue for most men and women. Parents of children born with meningomyelocele and spinal cord defects now can anticipate that their children's rehabilitation can include sex information which puts the spinal cord injured adolescent into an active role. Extensive experience from many centers over recent years confirms this. Yet, how can these things be true for those persons who have sensorimotor losses preventing transmission of genital sensation to the brain, experiences of physical orgasm, external ejaculation, psychogenic penile erections or vaginal lubrications, or who have indwelling catheters or bowel incontinence?

At the University of Minnesota, we have learned that several changes in the physician's approach to a patient with a spinal cord injury have made a major difference. First, we have learned to view sex as only a part of sexuality and sexuality as an important health issue, deserving active and sensitive attention. Sexual adjustment after spinal cord injury is now a part of the treatment plan just as much as bladder function or spinal stability training or education in the activities of daily living.

Second, we have learned that sexuality is not equated with genitality or procreation. Genital pleasuring is only one form of sexual expression and sex for recreation is more common than sex for procreation.

Third, great human energies can be locked up or freed by sexuality. These energies are capable of propelling a person with a damaged spinal cord forward into a job and a productive life or oppressing his sense of self-esteem and adding a new disability onto the motor and sensory paralysis.

Fourth, mobility and communication usually are linked together in the able-bodied state. After injury to the spinal cord, persons learn that effective communication can compensate greatly for loss of mobility. And sexuality is a potent communication tool to be used wisely and with respect.

Last, as Weiss and Diamond have shown, realistic acceptance of physical disability often is best seen in those who have a realistic acceptance of their sexuality. For physicians, sexuality no longer need be considered a difficult subject to include in the rehabilitation process; it is in fact a facilitating one.

Which direction a person with spinal cord

damage will take after treatment in a spinal center may depend not only on his neurologic, orthopedic, urologic and physiatric status but also on his or her sexuality.

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REFERENCE

Weiss AJ, Diamond MD: Sexual adjustment, identification, and attitudes of patients with myolopathy. Arch Phys Med Rehabil 47:245-250, Apr 1966

Manipulation

THE LAYING ON OF HANDS and the manipulation of somatic tissues and osseous articulations is one of the oldest and most widely used methods of treating patients. Reference to manipulation can be found in the records of most ancient civilizations, including the Greeks, Romans, South American Indians and Eskimos, and was discussed in the works of both Hippocrates and Galen. Reasonable estimates suggest that between 5 percent and 10 percent of the population of the United States will receive some form of manipulative therapy each year.

Definition

The term manipulative therapy is used to include all procedures whereby hands are laid on the body with a therapeutic purpose. Such procedures as massage, manual trigger point or myofascial manipulation, and manual traction are included under this heading along with the more classic long lever joint manipulation and mobilization techniques, and the specific short lever dynamic thrusts referred to as joint or spinal adjustments.

Clinical Efficacy

In recent years there has been a substantial increase in the amount of clinical research being conducted into spinal manipulation. It appears that manipulation can cause significant immediate improvement of acute low back pain when compared with placebo treatment, bed rest and analgesia or simple laying on of hands. There are a number of reports of successful management of other acute and chronic spinal pain syndromes; referred pain syndromes such as cervical, brachial and dorsal neuralgias and sciatica; a variety of headaches, especially those related to muscle tension or cervical trauma; and a number of other often vaguely defined disorders.

Complications

Complications of spinal and peripheral joint manipulation are extremely rare when one considers that more than 90,000,000 manipulations are given in the United States each year. Most complications that have been reported fall into the categories of missed bony pathologic conditions such as metastatic disease or fractures, compromise of the vertebrobasilar arterial system, herniation of intervertebral discs and minor soft tissue trauma. The greatest protection against these complications is for manipulation to be attempted only by clinicians with sufficient diagnostic acumen to recognize the contraindications and with adequate skill and experience in the various manipulative techniques that can be applied.

Theoretical Basis

The theories of manipulation fall into two major categories. The biomechanical theories deal with the effect of the manipulation on synovial joints, intervertebral discs, muscles and ligaments. The neurological theories describe the reflex effects of stimulating somatic receptors, the various components of pain and the pathophysiology of nerve compression. Recent international conferences such as those edited by Goldstein, Buerger and Tobis, and Korr have used an interdisciplinary approach to the investigation of the clinical efficacy and theoretical basis of manipulation which greatly increases our understanding of what happens when the hands are used as a therapeutic tool.

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REFERENCES

Goldstein M (Ed): The Research Status of Spinal Manipulative Therapy, NINCDS Monograph No. 15, Publication No. (NIH) 76-998. US Department of Health, Education, and Welfare, Bethesda, MD, 1975

Buerger AA, Tobis JS (Eds): Approaches to the Validation of Manipulation Therapy. Springfield, IL, Charles C Thomas, 1977

Korr IM (Ed): The Neurobiologic Mechanisms in Manipulative Therapy. New York, Plenum Press, 1978

The Hazards of Exercise in Patients With Weakness of Neuromuscular Origin

IT IS A WELL-KNOWN and accepted fact that long-term strenuous exercise will increase the functional capacity (strength or endurance, or both) of normal muscles. The training programs necessary for athletic excellence are good examples of this fact.

The question is how much exercise is appropriate for patients with muscles weakened by neuromuscular disorders. Normal muscle is capable of producing considerably greater force than is ever generated by voluntary contraction under normal circumstances. It is generally accepted

that a muscle must lose more than 50 percent of its capacity before it can be clinically identified as weak. It is assumed that the extra 50 percent is present as a reserve to permit muscles to function for prolonged periods, providing the endurance necessary for normal activities such as walking. With this concept, any muscle that is clinically weak due to a neuromuscular disorder has lost its reserve capacity. Recent studies have shown that in muscles from experimental animals made weak by neuromuscular disease or by artificial means there is evidence of damage on physiologic and histologic testing following exercise. Therefore, is a *strengthening* exercise program beneficial or harmful for these patients when normal activity requires near maximum effort from their weakened muscles?

It is well-known that serum levels for the muscle enzyme creatine phosphokinase can increase to values several times normal levels following exercise in normal persons as well as in patients with weakness. Many of us have also seen examples of myoglobinuria in otherwise normal persons following strenuous exercise. Both suggest the possibility of muscle injury from exercise. This is not intended to suggest that all exercise may be injurious to patients with muscle weakness. Muscle function will deteriorate with disuse and this is exaggerated in patients with weakness due to neuromuscular disorders. Therefore, some activity is essential. This information does not allow us to state how much exercise is appropriate for patients with muscle weakness; however, it does suggest that caution must be used in prescribing strengthening exercises for patients with neuromuscular weakness.

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REFERENCES

Reitsma W: Skeletal muscle hypertrophy after heavy exercise in rats with surgically reduced muscle function. Am J Phys Med 48:237-258, Oct 1969

Taylor RG, Fowler WM, Doerr L: Exercise effect on contractile properties of skeletal muscle in mouse muscular dystrophy. Arch Phys Med Rehabil 57:174-180, Apr 1976

Walton JN (Ed): Disorders of Voluntary Muscle, 3rd Ed. Edinburgh, Churchill Livingstone, 1974

Sex Counseling for Postmyocardial Infarction Patients

UPON RECOVERY from an acute myocardial infarction, a patient all too frequently is told to rest at home for two weeks, gradually increase activity over the next four weeks and then return to his occupation. Often the last direction is "Take it easy."

In giving directions, seldom does a physician broach the subject of sexual function. If the subject is raised by the patient, discussion is usually cursory or avoided. Today, it is an accepted maxim that discussion about sexual activity is as important as advice about diet, exercise or any other biologic activity. Fears, hearsay and misconceptions make the decision regarding sexual intercourse difficult for both cardiac patient and mate. Lacking professional advice, patients may have apprehension with resulting anxiety, personal frustration and general unhappiness. The physician should encourage an open discussion with both patient and mate. Specific guidelines and details dispel the fear and anxiety.

The expenditure of energy in healthy subjects has been studied by Hellerstein. During foreplay, there is a skin flush with a sense of warmth and a gradual increase in the respiratory rate, heart rate and blood pressure. The physiologic measurements return to normal abruptly after orgasm. Electrocardiographic changes are infrequent, but may show transient S-T depression and some degree of arrhythmia.

Is there danger of sudden death? Very little. Ueno, the Japanese pathologist, carried out 5,559 autopsies in cases of sudden death over a period of four years. Of these, only 34 of the patients died during coitus; all of these patients had had severely damaged hearts.

Proper positioning permits satisfactory intercourse when partners understand that assuming a given position can minimize strain on the heart patient. The recommendation is that the mate assume the role of the active partner from intromission through orgasm. In most uncomplicated cases of acute myocardial infarctions, patients can resume their normal sexual activity four to six weeks after discharge from hospital. If the patient can exercise a level of 6 to 8 calories per minute, such as vigorous walking, it is generally safe to recommend that he can resume sexual activity. In those patients who have complications of chest pain, serious ventricular arrhythmias and pump failure, coitus must be denied or greatly curtailed both as to frequency and active participation.

Counselors should discuss with patients the increased danger after a meal; reaction to alcohol, which increases the heart rate and drops the blood pressure, and hazards of extremes in temperature, fatigue, tension, and furtive, anxious conditions with time restrictions.

Patients take great satisfaction in returning to

a normal way of life. Complete understanding between partners is inherently necessary. Then, a loving unhurried sexual relationship can bring matchless contentment.

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REFERENCES

Hellerstein HK, Friedman EH: Sexual activity and the post-coronary patient. Arch Intern Med 125:987-999, Jun 1970

Ueno M, cited by Branton M: Sex and the Heart. New York, Coward McCann, 1968, pp 26-27

Advances in Bladder Rehabilitation

FOR SPINAL INJURY PATIENTS an ideal bladder is free from an indwelling catheter, infection and autonomic dysreflexia. He or she should be able to have adequate, easy voiding and a normal genitourinary tract. The use of intermittent catheterization in establishing a reflex bladder is successful in about 70 percent to 90 percent of patients. Prolonged intermittent catheterization (20 weeks or more) is expensive and frustrating for patients and is usually associated with a dysfunctional neurogenic bladder. Patients without a balanced bladder following intermittent catheterization are also prone to silent renal damage. All such failures usually are due to detrusor-sphincter dyssynergia or increased urethral resistance, or both. Increased urethral resistance can be due to bladder neck and posterior urethral fibrosis, urethral strictures or an enlarged prostate. Inadequate opening of the bladder neck and posterior urethra during voiding can also be due to bladder-bladder neck dyssynergia or bladder-external sphincter dyssynergia. Dyssynergia between bladder and bladder neck usually results from increased alpha adrenergic activity. This can be shown on cystometrographic and urethral pressure profile studies before and after intravenous administration of phentolamine. In such patients a rise in blood pressure during cystometrographic studies also occurs. Dyssynergia between detrusor (bladder) and external urethral sphincter (periurethral striated muscles) can be shown on simultaneous cystometrographic and periurethral striated electromyography. All high paraplegics (above T5) and quadriplegic persons whose conditions are complicated with dyssynergia usually also have autonomic dysreflexia. Urodynamic studies involving simultaneous cystometrographic and pelvic floor electromyographic studies, flow rates, urethral pressure profile and voiding cystourethrographic studies (radiologic) may lead to the diagnosis of urethral "plumbing" problems.

Transurethral external sphincterotomy and bladder neck incisions can relieve obstructive urethral pathology and provide adequate voiding in such patients. This leads to pronounced improvement in bladder configuration, relief from vesicoureteral reflux, amelioration of autonomic dysreflexia and also significant improvement in hydronephrotic renal pelvicalcyceal system. Routine urodynamic studies in patients with inadequate voiding could provide an early diagnosis of detrusor-sphincter dyssynergia and bladder neck obstructive problems and thereby make it possible to prevent urologic complications.

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REFERENCES

Rossier AB, Ott R: Urinary manometry in spinal cord injury: A follow-up study—Value of systo-sphincterometrography as an indication for sphincterotomy. Br J Urol 46:439-448, Aug 1974

Perkash I: An attempt to understand and to treat voiding dysfunctions during rehabilitation of the bladder in spinal cord injury patients. J Urol 115:36-40, Jan 1976

Perkash I: Detrusor-sphincter dyssynergia and dyssynergic responses: Recognition and rationale for early modified transurethral sphincterotomy in complete spinal cord injury lesions. J Urol 120:469, 1978

Perkash I: Pressor response during cystomanometry in spinal injury patients complicated with detrusor sphincter dyssynergia. J Urol 121:778, Jun 1979

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EDITORIALS

How Much Freedom Do We Really Have?

It was 203 years and one month ago that the American people determined to be free and independent, and not bow to anybody. Millions of people have since come to these shores seeking fulfillment of the American dream for themselves and their children. Most have come legally, some illegally; all sought greater freedom and a better life. Much was achieved, many wrongs were corrected and Americans came to enjoy the world's highest standard of living. But now, 203 years after our Declaration of Independence, things seem at odds with our cherished traditions of freedom and independence. We find ourselves being shackled by internal controls, and external ones as well. Within the country we are at the mercy of a huge governmental bureaucracy which no one seems able to control. Internationally we find ourselves at the mercy of a few remote and apparently merciless foreign sheiks. One can certainly ask how much freedom and independence we really have in August 1979. The answer has to be that both our freedom and our independence are considerably less than they were.

In all fairness the world is much different than it was in 1776. Modern transportation and communication have made it smaller, and its workings have become far more complex. Technological, social, economic and political interdependence has crept up on us inexorably as science, industry and communications have progressed, which is something the founding fathers did not and perhaps could not foresee. While independence and interdependence may not be exact opposites, they nevertheless encroach upon one another—with freedom and independence often at a disadvantage in an encounter with the reality of interdependence and the need for some sort of controls for the smooth operation of an interdependent and complex society.

Our system of governance seems ill adapted to deal with complex problems of the kind we face. Whether in medicine or in government our leaders often have practical difficulty in looking beyond the next election, yet both the desired freedom and the necessary controls have longitudinal dimensions in time as well as their horizontal dimensions at any given moment. The legislative attempts to regulate interdependence on the one hand and to enhance freedom and recourse for the individual citizen on the other, do not easily keep up with rapidly changing events. Moreover, they have produced a paralyzing morass of conflicting laws and legal interpretations by the legislative, executive and judicial branches at the local, state and national levels of government. We are at the mercy of a system of governance that seldom considers the long-term consequences of its actions and whose principal tool for solving problems is simply to impose laws and regulations, and more laws and more regulations upon the citizenry.

Some new approach seems necessary. Without it freedom and independence will become even more of a travesty. The issues are now being hammered out in medicine and health care. There is still autonomy and independence for both doctors and patients. There is informed consent, which means agreement as to what will be done and therefore a commitment to work toward getting it done among free and independent persons and agencies who are nevertheless made interdependent by the circumstances of a medical problem. The process is not one of regulation or control, but rather one of collaboration among all who are properly concerned in order to solve an identified and defined problem. If freedom and independence are compromised, it is done freely by those involved, for an agreed upon course of action to address a particular problem at a particular time, and not in perpetuity as by a law. Perhaps some way can be found to extrapolate this simple freedom-preserving approach

to the problems of interdependencies among independent and autonomous institutions, public and private, in health care and in society. The emphasis would be more on consensus than on rule. This approach could result in a better answer to the question "How much freedom do we really have?"

—MSMW

Routine Spirometric Testing and COPD

THERE IS A REASONABLY well delineated clinical syndrome that is characterized by severe progressive airflow obstruction and that results from some combination of pulmonary emphysema and intrinsic narrowing of the airways. Because it is often difficult to determine how much of the airflow obstruction results from emphysema and how much from intrinsic airways disease (chronic obstructive bronchitis), the noncommittal diagnostic term chronic obstructive pulmonary disease (COPD) was introduced to describe this syndrome. While the term may have some usefulness in clinical practice, there is little justification for broadening its application. To do so can lead to increased confusion in a field already beset with semantic problems. Thus, I am concerned with the tendency to equate any obstructive ventilatory abnormality with COPD and to assume tacitly that a mild spirometric abnormality discovered on a screening test or in an epidemiologic study represents an early stage of a disease that will progress to severe disability.

The potential problem is well exemplified by the term chronic bronchitis. This term is often used by clinicians, especially in the United Kingdom, to classify patients who are disabled as a result of persistent airways obstruction and who have long histories of productive cough. In an attempt to study the early stages of this disease, chronic bronchitis was defined for epidemiologic purposes solely in terms of the productive cough, and it was assumed that factors related to this symptom would prove to be determinants of the more severe clinical disease to follow. It has now been shown, however, that smokers with epidemiologically defined chronic bronchitis have no greater rate of decline in lung function than other smokers.[1] Therefore, epidemiologically defined chronic bronchitis may not even be a significant risk factor for the clinical entity that bears the same name.

Is it possible that the same situation exists in COPD? How good is the evidence that mild abnormalities in lung function detected on screening tests or in epidemiologic studies will progress to a disabling clinical disease? These and several other questons must be examined in order to evaluate the recommendations regarding regular spirometric examinations that have been made by Dr. Buist in her review of risk factors for COPD elsewhere in this issue.

We do know that if one observes a large number of subjects over several years, those with the lowest average values for one-second forced expiratory volume (FEV_1) will tend to show the greatest rates of decline in FEV_1.[1] The relationship is statistically significant, but there is very wide variability in the data. Those with initially low values may progress at a normal rate rather than having a rapid decline. In fact, even after multiple measurements over many years, the mean FEV_1 explains only a small portion of the variability in observed rates of decline. These data raise serious doubts about the ability of a single FEV_1 measurement to predict subsequent course. Although one may suspect that a subject with a slightly low FEV_1 at age 30 or 40 years is at some increased risk of later COPD, the degree of this risk is totally unknown. Further, some of the impairment noted on screening spirometry is responsive to bronchodilator medication and probably represents an asthmatic-like condition.[2] The relationship of this type of finding to subsequent disabling COPD is totally unknown.

As far as annual measurements are concerned, trends determined from such observations are notoriously unreliable. Even after using sophisticated statistical manipulations to refine their data, and even after many years of observations, Fletcher and his associates[1] place little confidence in their calculations of rates of decline in individual subjects. Under the best test circumstances the FEV_1 is a quite variable measurement, and its variability far exceeds the expected annual decline even for smokers.

Even if short-term trends could be measured with precision, their interpretation is uncertain. Little is known about long-term fluctuations in spirometric test results and about the preclinical natural history of COPD. It is possible that rates of decline in FEV_1 show pronounced variability throughout adult life. It even remains possible

that cases of disabling COPD can develop as a result of a very rapid decline in lung function over the five to ten years preceding the onset of clinical symptoms. There is no assurance, therefore, that a smoker with a normal FEV_1 at age 40 years cannot subsequently undergo a very rapid decline in lung function and develop disabling COPD by the age of 60 years, nor can we be sure that a rapid rate of decline in lung function observed between the ages of 30 years and 35 years will persist for a lifetime and lead to disabling disease.

In view of all of these uncertainties, it would be well to distinguish mild ventilatory abnormality discovered on routine spirometric screening from COPD and to reserve judgment about the extent to which one can predict subsequent disease from spirometric tests.

Even if one does accept the concept that a slightly low FEV_1 does identify the patient at high risk of later COPD, of what use is this information? Clearly, it can be used to reinforce smoking cessation efforts. But how good is the evidence that smoking cessation after development of a low FEV_1 is effective in preventing later COPD? We do know that the excessive decline in lung function of the average smoker generally stops with smoking cessation.[1] There is no direct evidence, however, that this is true of that special group of smokers in whom COPD develops. Smoking cessation after the development of clinical symptoms does not prevent further progress of the disease,[3] and in many patients symptoms first appear well after smoking has been discontinued.[4] Furthermore, death rates from chronic respiratory disorders (unlike most other smoking related diseases) do not show a significant decline within ten years of stopping smoking in a longitudinal study of British doctors.[5]

There are certain facts that are much better established than the significance of mild spirometric abnormalities. We know that cigarette smokers have a much higher overall death rate than nonsmokers and that the majority of this excess mortality results from cardiovascular disorders. Much of the remaining excess mortality can be ascribed to lung cancer and to a variety of miscellaneous diseases. A relatively small fraction of the risk of smoking is related to COPD. Consequently, every effort should be made to induce patients to stop smoking cigarettes regardless of their lung function level. If discovering a low FEV_1 can help in this effort, routine tests may serve a useful purpose, and I agree that spirometry should be part of any overall health evaluation. On the other hand, the effect can be negative if a normal spirogram is mistakenly used as evidence that a patient is not susceptible to the multiple adverse effects of smoking on health, thereby reinforcing his smoking habit. Also, if minor spirometric abnormalities or changes in spirometric measurements are overinterpreted, there is risk of creating disease in a person who previously considered himself healthy.

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REFERENCES

1. Fletcher C, Peto R, Tinker C, et al: The Natural History of Chronic Bronchitis and Emphysema. Oxford, Oxford University Press, 1976

2. Lorber DB, Kaltenborn W, Burrows B: Responses to isoproterenol in a general population sample. Am Rev Resp Dis 118: 855-861, 1978

3. Burrows B, Earle RH: Course and prognosis of chronic obstructive lung disease. N Engl J Med 280:397-404, 1969

4. Burrows B, Niden AH, Barclay WR, et al: Chronic obstructive lung disease: I. Clinical and physiological findings in 175 patients and their relationship to age and sex. Am Rev Resp Dis 91:521-540, 1965

5. Doll R, Peto R: Mortality in relationship to smoking: 20 years' observations on male British doctors. Br Med J 2:1525-1536, 1976

Tel-Med

THE SUCCESS of Tel-Med, reported elsewhere in this issue, is indeed a bright spot in the relationships of organized medicine with the public. The San Bernardino County Medical Society is to be commended for its leadership and real accomplishment.

The list of the 15 most requested tapes is interesting and may be telling us something about what patients and the public want to know but may be afraid to ask. The anonymity of Tel-Med may be providing a window to these important but often unexpressed fears and needs for authoritative information on the part of troubled persons. Sexuality in its various aspects accounts for eight of the 15 most requested tapes and shows the depth of concern with this topic in these times. The present emphasis on human sexuality in medicine and patient care is certainly timely if not overdue. The others, as might be expected, reflect a variety of health concerns which seem to be more or less in the public eye.

The lesson for practicing physicians is that their

patients are likely to have some of these same concerns but do not speak of them, and therefore are not relieved of some fear or need to know. At the very least physicians should be aware of the nature of the most requested topics in the Tel-Med experience, and sensitive to any indication of need for information on these subjects by their patients.

—MSMW

More Effective Use of Antidepressants

ELSEWHERE IN THIS ISSUE appears a Medical Progress article, "Recent Advances in Antidepressant Drug Treatment," by Stephen E. Ericksen, MD.

Antidepressant drugs were not enthusiastically received during their first decade of use. Controlled comparisons of both tricyclics and monoamine oxidase (MAO) inhibitors either showed no difference from placebo or a trivial one, as many depressed patients remitted spontaneously. I summarized this literature in a 1966 editorial entitled "Antidepressants: A Somewhat Depressing Scene."[1] In retrospect, this pessimism was unwarranted due to two errors that were even then being recognized.

The heterogeneity of depressive reactions was a major problem. Although a plethora of terms denote the various types of depressions, most early studies assumed that antidepressants were universally effective. Failure to show differences between antidepressant drugs and placebo was common in studies using unselected groups of depressed patients. This difficulty was partially resolved by the recognition that patterns of symptoms and signs of depressed patients could be used to make diagnostic distinctions. This approach led to identification of a subgroup of depressed patients who responded specifically to tricyclic antidepressants.[2] Not surprisingly, these patients had characteristics resembling those of so-called endogenous depressions, a group that had been reported as specifically responsive in the initial clinical trial of imipramine.[3]

Most clinicians now agree that tricyclics are specifically effective in endogenous depression. Whether such selectivity applies to MAO inhibitors is less certain. The high success rate of the latter drugs in neurotic depressions is clouded by the high rate of placebo response found in this group. Anecdotal evidence suggests that patients with depressions characterized by high levels of anxiety, hypochondriasis and obsessive-compulsive-phobic features may respond specifically to MAO inhibitors, as noted in Dr. Ericksen's paper. Such selectivity of action of MAO inhibitors has been difficult to assess because these agents are not commonly used in clinical practice.

Biochemical classification of depressions has been recently attempted. Both serotonin and norepinephrine may be involved in the amine hypothesis of depression, some investigators favoring one transmitter, others, the other. This dilemma has been neatly solved by suggesting that a functional deficiency of both noradrenergic and serotonergic neurotransmission may be involved in endogenous depression. Distinctions are made by the pattern of excretion of the norepinephrine metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG). This metabolite is more derived from central nonadrenergic activity than any other urinary metabolite of norepinephrine, such as normetanephrine or vanilmandelic acid. *Low* excretion of MHPG is presumed to represent deficient nonadrenergic activity, while *high* excretion is believed to represent deficient serotonergic activity. Reciprocal levels of the serotonin metabolite, 5-hydroxy-indoleacetic acid and MHPG in cerebrospinal fluid also suggest such a relationship.

The importance of making distinctions between the two neurotransmitter subtypes of depression hinges upon the idea that various tricyclics differ in selectively blocking uptake of these two neurotransmitters. Amitriptyline is at present the most specific blocker of uptake of serotonin while desipramine is most selective in blocking uptake of norepinephrine. The appeal of MHPG determinations as a way to classify depressions is based on the possibility that the most efficacious drug for any given patient might be predated. Although preliminary data suggest this to be the case, they are still fragmentary.[4]

Unfortunately, MHPG excretion is no different in patients with affective disorders than in normal persons. The usual daily excretory rate, both in depressed patients as well as in normal persons, usually ranges between 900 and 3,500 μg per 24 hours.[5] Such values account for more than 90 percent of these reported in patients with affective disorders. One can think of no other precedent in all of medicine in which a diagnostic classification

of patients can be made on the basis of variations within the normal range of values for a laboratory test.

A second reason for the disappointing early results with antidepressant drugs was probably inadequate doses. As clinical experience developed it became apparent that in some, although by no means in all, patients a daily dose of 150 mg or more of imipramine or amitriptyline was needed to obtain optimal effects. Likewise doses of the MAO inhibitor, phenelzine, in the order of 60 to 90 mg per day are required for full therapeutic effect. Many of the early studies of these drugs used smaller doses, ones that would be only partly efficacious, if at all.

Determination of plasma concentration of tricyclic antidepressants has been proposed as a way to assure adequate dosage. For a variety of reasons, the same dose of tricyclic antidepressant may produce widely different steady-state plasma concentration of drug among different persons. It is still not certain whether or not a therapeutic range of plasma concentrations can be established for these drugs. Nortriptyline, although not widely used, has been most extensively studied. A therapeutic range of 50 to 150 ng per ml has been proposed for that drug. Imipramine has been less intensively studied, but the present feeling is that plasma concentrations less than 120 to 150 ng per ml of combined imipramine/desipramine (most of the drug is converted to its secondary amine metabolite) are likely to be ineffective.[6]

Such correlations between clinical effects and plasma concentrations are confounded by a number of problems. First, tricyclics are highly protein-bound so that slight shifts in the degree of protein-binding may vastly alter the amount of pharmacologically active, unbound drug even *with no change in total plasma concentration.* Second, many of the drugs produce hydroxylated metabolites which retain pharmacological activity. In the case of nortriptyline, the 10-hydroxy metabolite is usually more abundant than the parent drug. The assumption that the hydroxy metabolites are conjugated, and therefore inactive, may not be true. Third, technical problems of how the blood samples are obtained and how much contact they have with the stoppers of tubes may produce inconsistent artifacts in determination of plasma concentrations of nortriptyline.

Determination of plasma concentrations of tricyclic antidepressants should probably best be done on a selective basis rather than as a routine monitoring. The following indications are suggested:

- Failure of a patient to respond to doses in the range of 75 to 150 mg per day. A very low plasma concentration may suggest poor bioavailability or, more likely, non-compliance.
- A decision to use larger than usual doses, such as those greater than 250 mg per day. Having some record of drug levels shows a proper degree of concern about such intensive treatment.
- Treatment of very old or very young patients should be conservative. Such patients have decreased protein-binding of tricyclics and more unbound, active drug. Plasma concentrations should be deliberately kept on the low side in such patients. Older patients also tend to get higher peak and steady-state levels, possibly because they clear the drug less rapidly.
- The presence of concurrent illness that may interfere with drug clearance, such as liver disease, would merit checking plasma concentrations. An illness that may be seriously aggravated by the drug, such as heart disease, might also merit determination of plasma concentrations, although one may prefer electrocardiographic monitoring.
- Plasma concentration may help explain some questionable adverse reactions.
- The decision about when an overdosed patient is fully recovered may be helped by determining if the plasma concentration of drug has returned to the therapeutic range.

With careful attention to the diagnosis of depression, it is likely that antidepressant drugs may be used in fewer patients but with better results. By using adequate doses of these drugs, one may eliminate a major cause of treatment failures. These are the major lessons we have learned in how to use these drugs more effectively.

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REFERENCES

1. Hollister LE: Editorial. Antidepressants—A somewhat depressing scene. Clin Pharmacol Ther 6:555-559, 1965
2. Overall JE, Hollister LE, Johnson M, et al: Nosology of depression and differential response to drugs. JAMA 195:946-948, 1966
3. Kuhn R.: The treatment of depressive states with G22355 (imipramine hydrochloride). Am J Psychiatry 115:459, 1958
4. Beckmann H, Goodwin FK: Antidepressant response to tricyclics and urinary MHPG in unipolar patients. Arch Gen Psychiatry 32:17-21, 1975
5. Hollister LE, Davis KL, Overall JE, et al: Excretion of MHPG in normal subjects—Implications for biological classification of affective disorders. Arch Gen Psychiatry 35:1410-1415, 1978
6. Risch SC, Huey LY, Janowsky DS: Plasma levels of tricyclic antidepressants and clinical efficacy: Review of the literature. J Clin Psychiatry 40:9-21, 58-69, 1979
7. Hollister LE: Monitoring tricyclic antidepressant plasma concentrations. JAMA 241:2530-2533, 1979

CASE REPORTS

Refer to: Hirasuna JD, Shelub I, Bolt RJ: Hyperhistaminemia and peptic ulcer. West J Med 131:140-143, Aug 1979

Hyperhistaminemia and Peptic Ulcer

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INCREASED CIRCULATING HISTAMINE LEVELS have been found in a number of disease states including bronchial asthma, some allergic conditions, cutaneous burns and eosinophilia from various causes. Using Code's modification[1] of the method of Barsoun and Gaddum, normal values have been established at between 1.08 and 8.5 μg, expressed as free histamine base per dl whole blood. In the above diseases, elevated values are seldom more than 20 μg per dl. In the myeloproliferative diseases there are numerous reports of unusually high levels—that is, more than 100 μg per dl and as high as 2,000 μg per dl. Reports appeared in the American literature in 1937,[1] in the French literature in 1937[2] and in the German literature in 1941.[3] Since then results of numerous studies have confirmed these observation;[4-13] however, symptoms and signs resulting from the pharmacologic effects of hyperhistaminemia rarely have been recognized.

Gilbert, Warner and Wasserman[14] in 1966 were the first to report cutaneous and gastrointestinal symptoms associated with polycythemia vera and hyperhistaminemia. They noted a rough correlation between the number of basophils, histamine level, and the presence of pruritus, urticaria and gastrointestinal symptoms. They also reported relief of pruritus and urticaria with the antihistamine, cyproheptadine hydrochloride, despite a lack of change in histamine levels in the blood. There was no mention of the effect, if any, on gastrointestinal symptoms. Their studies indicated that there was little relief with the use of other medications including diphenhydramine hydrochloride, tripelennamine hydrochloride, chlorpheniramine, trimeprazine tartrate, chlordiazepoxide hydrochloride, meprobamate and prednisone. Moreover, the authors pointed out that pharmacologic effects of hyperhistaminemia were not uncommon in polycythemia vera, but seldom seen in chronic myelogenous leukemia, and they felt that this might be due to differences in binding of the histamine within the cell or in the rate of release of the histamine from the cell.

The first report of histamine symptoms in chronic granulocytic leukemia similar to those seen in systemic mast cell disease was reported in 1973 by Youman and co-workers[15] from the Mayo Clinic. The patient in their report had chronic granulocytic leukemia with basophilia (basophil count as high as 91,250 per cu mm), intense and disabling pruritus, cold urticaria and epigastric discomfort. Total blood histamine levels in this patient exceeded previously reported levels, reaching as high as 5,000 μg per dl on one occasion. Gastric analysis showed concentrations comparable to maximum histamine stimulation testing. However, upper gastrointestinal x-ray studies did not document peptic ulceration despite the high histamine levels. Pruritus and urticaria partially responded to treatment with diphenhydramine hydrochloride and brompheniramine maleate.

The first report of documented peptic ulceration associated with hyperhistaminemia and chronic granulocytic leukemia appeared in 1976.[16] In a patient admitted to the National Institutes of Health, gastric secretory levels strongly suggestive of the Zollinger-Ellison syndrome with normal serum gastrin levels were found.[16] A large actively bleeding postbulbar ulcer and two smaller duodenal ulcers, as well as a benign gastric ulcer, were seen on endoscopy. The patient's condition was unresponsive to the usual therapy for ulcer management but symptoms improved following oral administration of metiamide, 400 mg every four hours. The acid secretory rate fell from 6.5 mEq per 15 minutes to levels compatible with persistent achlorhydria for a period of 2½ hours following administration of metiamide. Unfortunately the patient died of leukemia within a few

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Figure 1.—X-ray film of the upper gastrointestinal region showing two ulcers **(arrows).**

weeks after treatment was started. At autopsy a healed ulcer, 0.3 cm by 1.0 cm, in the second portion of the duodenum was noted.

The following is the first documented case of chronic myelogenous leukemia with hyperhistaminemia, maximum gastric secretory activity, and multiple gastroduodenal ulceration responsive to administration of the histamine H_2 receptor blocking agent cimetidine.

Report of a Case

Acute promyelocytic leukemia was diagnosed in a 40-year-old man in July 1976. Chemotherapy was carried out and there was remission of all symptoms. In January 1977 findings on bone marrow studies were felt to be within normal limits; however, in March 1977 another bone marrow study showed a relapse with 40 percent blasts. In April 1977 bone marrow cytogenetics showed the Philadelphia chromosome and the diagnosis was changed to chronic myelogenous leukemia. On June 9, 1977, the patient was seen in the outpatient department, with complaint of itching and a skin rash. The following day he noted abdominal pain in the epigastric region accompanied by anorexia. Because of an apparent relapse of leukemia and the onset of abdominal pain, the patient was admitted to hospital on June 12, 1977.

On physical examination at the time of admission the following findings were noted: erythematous crusting lesions with multiple excoriations; blanching urticarial lesions; the liver was enlarged 5 cm below the right costal margin but the spleen was not definitely palpable. All blood studies and urine analyses gave findings within normal limits, other than a leukocyte count of 48,200 per cu mm with 50 percent basophils and elevated levels of alkaline phosphatase (93 units per liter) and lactic dehydrogenase (484 units per liter). Because of persistent and increasing abdominal pain, an upper gastrointestinal x-ray study was done (Figure 1). Two ulcers were easily seen, one in the superior portion of the antrum (1 cm in diameter) and another in the duodenal bulb (3 cm in diameter). Gastric analysis with maximum betazole hydrochloride (Histalog) stimulation showed a pronounced hypersecretory state (Table 1).

The patient was placed on a regimen of antacids consisting of magaldrate (Riopan), 60 ml per hour. Treatment with hydroxyurea was started for the relapse of leukemia. The patient noted no relief of abdominal pain and, while treatment was under way, massive upper gastrointestinal hemorrhage developed. Multiple blood transfusions were necessary to maintain the hematocrit at acceptable levels. Upper gastrointestinal endoscopy at this time showed a 1 cm benign appearing antral ulcer surrounded by edema and hyperemia. In addition, a large ulcer in the duodenal bulb covered by fresh blood clot was seen. Several hours after endoscopy, massive blood loss occurred again and the patient was taken to the operating room where hemigastrectomy and Bill-

TABLE 1.—*Results of Gastric Analysis With Maximum Betazole Stimulation*

	Basal		*After betazole**				
Time (minutes)	0-30	30-60	0-15	15-30	30-45	45-60	60-75
Volume	206.00	178.00	116.00	88.00	162.00	162.00	131.00
pH	2.20	2.10	2.20	2.50	2.10	2.20	2.60
Acid mEq/L	112.80	126.60	110.40	87.60	109.80	89.90	85.00
Acid output	23.24	22.53	12.81	7.71	17.79	14.55	11.56

BAO (basal acid output) = 45.77 mEq per hour
MAO (maximal acid output) = 56.71 mEq per hour
PAO (peak acid output) = 64.68 mEq per hour
BAO/MAO = 0.81

*1.5 mg per kg of body weight

TABLE 2.—*Gastric Analysis Two Weeks After Operation but Before Cimetidine Administration*

Time (minutes)	0-30	30-60
Volume	116.0	84.0
pH	2.2	2.2
Acid mEq/L	66.0	56.0
Acid output	7.6	4.7

BAO (basal acid output) = 12.3 mEq per hour

TABLE 3.—*Gastric Analysis After Two Weeks of Cimetidine Administration**

	Basal	*After betazole*†	
Time (minutes)	0-30	0-30	30-60
Volume	4.0	74.0	44.00
pH	7.6	5.4	3.30
Acid mEq/L	0.0	13.6	26.20
Acid output	0.0	1.0	1.15

BAO (basal acid output) = 0

*300 mg
†1.5 mg per kg of body weight

roth II anastomosis were done. Vagotomy was not technically possible because of massive hepatomegaly. Gastrin levels preoperatively at the time of gastric analysis were reported as 77 pg per ml (N = less than 100). Whole blood histamine level was reported as 2,376 μg per dl (N = 4 to 7). Despite the hemigastrectomy, gastric analysis two weeks after the operation showed a basal acid output of 12.3 mEq per hour with acid concentrations of 66 mEq per liter at between 0 and 30 minutes and 56 mEq per liter at between 30 and 60 minutes (Table 2). At the time of this study the leukocyte count was 76,400 per cu mm with 88 percent basophils. In view of this, administration of cimetidine, 300 mg four times per day, was started and the patient received 100 rads of total body irradiation to diminish the leukocyte count.

After two weeks of cimetidine therapy and when the leukocyte count was 52,100 per cu mm with 89 percent basophils, gastric analysis was repeated and a pronounced decrease in basal secretory rate was found (Table 3). Blast crisis was now treated successfully with cytosine arabinoside and 6-thioguanine and during the next three months the patient was without abdominal symptoms. On August 24, 1977, the leukocyte count was 8,500 per cu mm with 4 percent basophils and the total blood histamine level was 17 μg per dl. Administration of cimetidine was discontinued. In October 1977 the patient returned to the clinic complaining of midepigastric pain of several days' duration and one episode of coffee-ground emesis. The leukocyte count was 58,600 per cu mm with 68 percent basophils and the total blood histamine level was 6,591 μg per dl. Blast crisis was confirmed by bone marrow examination but treatment was initially withheld because of a concurrent cellulitis. Cimetidine therapy was started. The abdominal pain disappeared and there were no further episodes of gastrointestinal hemorrhage. The blast crisis was again successfully treated.

The abdominal pain remained in abeyance with cimetidine therapy until January 1978. The patient then presented to the outpatient clinic with midepigastric pain that had begun after his supply of cimetidine had run out. The pain again was easily controlled by administration of cimetidine and antacids but once more the leukocyte count (71,100 per cu mm with 53 percent basophils) was elevated and examination of bone marrow indicated blast crisis. Chemotherapy induced pronounced pancytopenia; pneumonia and Escherichia coli and Klebsiella sepsis developed, and the patient died. Postmortem examination was not permitted.

Discussion

This is the second reported case of hyperhistaminemia associated with chronic myelogenous leukemia resulting in severe gastrointestinal ulceration. Gastric secretory rate and basal acid output/maximal acid output ratios were similar to those seen in the Zollinger-Ellison syndrome. However, the stimulus to secretion was histamine rather than gastrin. Control of the gastric response to hyperhistaminemia was satisfactory with the use of the H_2 blocking agent cimetidine. With remission of leukemia and a decrease in basophilia, the histamine level decreased almost to normal. Hyperhistaminemia recurred with relapse, but gastrointestinal symptoms were controlled during cimetidine treatment.

Pharmacologic effects of hyperhistaminemia in patients with systemic mastocytosis have been reported frequently. Because the basophil is the only circulating myelocyte with a histamine content similar to that of tissue mast cells, it is difficult to explain why the syndrome of *hyperhistaminemia* has not been reported more frequently in association with the myeloproliferative diseases, particularly when significant basophilia exists. Conceivably, symptoms of pruritus, the presence of urticaria and varied gastrointestinal symptoms may be ascribed to the underlying myeloproliferative disease rather than to hyperhistaminemia. On the other hand, histamine effects may be rare

because histamine is tightly bound within the cell boundaries of the circulating basophils. Further studies of total blood histamine as well as plasma histamine levels and their correlation with gastric secretory rates in patients with myeloproliferative disease are needed. Determining levels of histamine, evaluating gastric secretory status and obtaining x-ray films of the upper gastrointestinal region in patients with myeloproliferative diseases should be given higher priority.

Summary

The mast cell (tissue) and basophil (circulating) are known to have high concentrations of histamine. Proliferation of mast cells (systemic mastocytosis) often results in hyperhistaminemia with resultant pharmacologic effects (pruritus, urticaria and the like). Similarly, proliferation of basophils (myeloproliferative diseases) is associated with hyperhistaminemia. It is odd that reports of pharmacologic effects of histamine on target organs (skin, lungs, heart and stomach) have been reported in rare instances only. This case of chronic myelogenous leukemia is the second that has been reported involving histamine stimulation of gastric acid secretion and peptic ulceration of a magnitude similar to the acid secretion resulting from hypergastrinemia. It is the first case showing adequate control of the hyperacid secretory state by cimetidine treatment. It is possible that pharmacologic effects of hyperhistaminemia in the myeloproliferative diseases is more common than the literature indicates.

REFERENCES

1. Code CF, MacDonald AD: The histamine like activity of blood. Lancet 2:730-733, 1937
2. Marcou I, Gingold N, Parhon CC Jr: L'histamine dans les maladies du sang. Bull Acad do méd de Roumaine 2:366-371, 1937
3. Went F, Rex-Kiss B: Ueber den Histaminhalt des Blutes bei Pathologischen Anderungen des Blutbildes und Blutdruckes. Z klin Med 139:157-162, 1941
4. Shimkin MB, Zon L, Crigler CW: Blood histamine in gastric cancer and peptic ulcer. Proc Soc Exp Biol and Med 52:335-338, 1943
5. Shimkin MB, Saperstein L, Goetzl FR, et al: Blood histamine in leukemia and erythremia. J Nat Cancer Inst 9:379-387, 1948
6. Thiersch JB: Histamine and histaminase in chronic myeloid leukemia of man—I. Histamine in the blood of chronic myeloid leukemia; II. Histamine and histaminase in the blood of myeloid leukemia under and after deep X-ray treatment. Aust J Biol and Med Sc 25:73-74, 75-77, 1947
7. Valentine WN, Lawrence JS: Studies on blood histamine partition of blood histamine before and after clotting in health and disease states. Am J Med Sc 216:619-624, 1948
8. Valentine WN, Pearce ML, Lawrence JS: Studies on the histamine content of blood with special reference to leukemia, leukemoid reactions and leukocytosis. Blood 5:623-647, 1950
9. Shimkin MB, Beirman HR, Low-Beer BVA, et al: Blood histamine in myelogenous leukemia. Cancer 4:570-578, 1951
10. Valentine WN, Beck WS, Follette JH, et al: Biochemical studies in chronic myelogenous leukemia, polycythemia vera and other idiopathic myeloproliferative disorders. Blood 7:959, 1952
11. Brandt L, Cederquist E, Rorsman H, et al: Blood histamine and basophil leukocytes in polycythemia. Acta Med Scan 176: 745-750, 1964
12. Horakova Z, Keiser HR, Beaven MA: Blood and urinary histamine levels in normal and pathological states as measured by a radiochemical method. Clin Chem Acta 79:447-456, 1977
13. McCarthy DM: Report on the United States experience with cimetidine in Zollinger-Ellison syndrome and other hypersecretory states. Gastroenterology 74:453-458, 1978
14. Gilbert HS, Warner RRP, Wasserman LR: A study of histamine in myeloproliferative disease. Blood 28:795-806, 1966
15. Youman JD, Taddeini L, Cooper T: Histamine excess symptoms in basophilic chronic granulocytic leukemia. Arch Int Med 131:560-562, 1973
16. Olinger EJ, McCarthy DM, Young RC, et al: Hyperhistaminemia and hyperchlorhydria in basophilic granulocytic leukemia. Gastroenterology 71:667-669, 1976

Refer to: Stochosky BA: Necrotic arachnidism. West J Med 131: 143-148, Aug 1979

Necrotic Arachnidism

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ARACHNIDISM IN NORTH AMERICA was first discussed in the medical literature of the United States in 1872.[1] It was not until 1957, however, that the first article discussing Loxosceles species of spiders as the probable cause of necrotizing bites in the United States was published.[2] Since then the number of presumed and proved cases of necrotic arachnidism has greatly increased. The cases reported have ranged from insignificant blebs,[3] through troublesome necrotic lesions, to serious necrosis complicated by hemolytic anemia, diffuse intravascular coagulation and death.[4-6]

Until about ten years ago necrotic arachnidism was thought to be a problem only in the midwestern United States, but then reports of similar lesions from southern and southwestern states began to appear.[7] The first case in Mississippi for example, was recorded in 1962, but by 1971 a total of 31 necrotic spider bites were reported there.[8] By 1966 necrotic arachnidism had occurred as far west as Los Angeles, as far north as Indiana and as far south as Baja California.[9] Dr. Findlay Russell of the University of Southern California, Department of Neurological Research, has recorded about ten cases of such bites in Southern California. With its increased incidence, knowledge of the natural history, physiology, diagnosis and treatment of this condition is becoming more important to physicians throughout the United States.

Report of a Case

A 23-year-old man awoke, after sleeping on the couch at his sister's house, with sudden pain in his right ankle. He tried to walk but fell be-

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cause of pain and dizziness. During the day he noted widespread muscle and joint pain which began in the right leg and thigh; nausea, fever and chills; tremor (greater in the arms); swelling and redness of the right foot, and a vesicle on the right ankle. These symptoms worsened.

The man went to the emergency room at the San Bernardino County Medical Center 12 hours after the symptoms began. A small vesicular lesion surrounded by 3 to 4 cm of erythema and induration was noted. It was felt that the cause was a spider bite. He was given medication for pain and sent home.

On his return 40 hours later the patient said that pain in his hip and shoulder joints was severe, as was pain at the site of the lesion. He was obviously distraught and there was a coarse tremor in the arms. Blood pressure was normal, temperature was 38.5°C (101.3°F) and pulse rate was 110.

On physical examination, the abdomen was mildly tender to palpation. There was no swelling, erythema, effusion or increased pain on palpation of the painful and stiff joints. The muscles, especially in the right thigh, were notably tender. On the lateral aspect of the ankle there was a 0.75 cm bullous lesion filled with clear fluid and layered white matter, surrounded by an irregular area measuring 8 cm by 15 cm of erythema and induration. The foot was held in plantar flexion and there was a pronounced decrease in the motion of all toes. Mild lymphadenopathy was found in the right inguinal region.

Because the patient was reluctant to be admitted to hospital, cloxacillin (Tegopen), 500 mg given orally every six hours, was prescribed and he was allowed to return home, with instructions to elevate his right foot. He was asked to return in 24 hours, or sooner if the lesion became worse. Specimens for complete blood count, analysis of urine and culture of the aspirate from the vesicle were obtained.

The patient returned 24 hours later, 78 hours after the onset of pain and erythema. There was a notable change in the appearance of the right foot (see Figure 1). The skin was taut with edema and induration, was slightly erythematous and was fixed in plantar flexion. In addition to the primary bulla, there were two adjacent irregular bullae, each about 3 cm in diameter. The right leg was swollen and erythematous up to the knee. The lateral part of the ankle was mottled with superficial hemorrhage, blebs, nonperfused

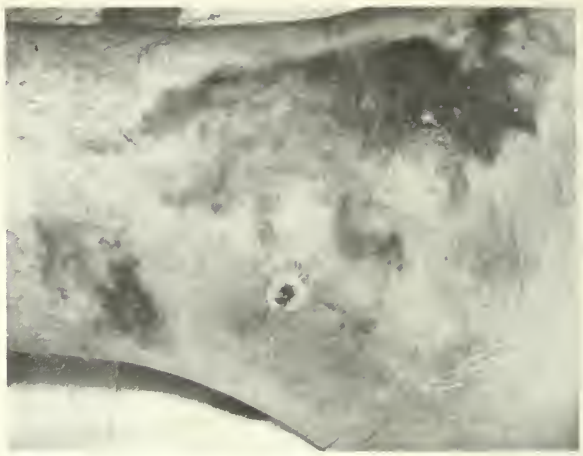

Figure 1.—Erythema, blebs, hemorrhage and ischemia occurring 78 hours after onset of symptoms.

skin and pronounced erythema. The pain was excruciating. Systemic symptoms of tremor, fever, nausea, anorexia and myalgia, although improved, were still present. The joint pain had become worse and walking was impossible. The leukocyte count was 19,400 per cu mm with 81 percent polymorphonuclear leukocytes, 16 percent bands, 7 percent lymphocytes, 1 percent monocytes and no eosinophils. Erythrocyte sedimentation rate was 36 mm per hour, blood urea nitrogen level was 11 mg per dl, creatinine level was 1.1 mg per dl, and analysis of urine showed 1+ proteinuria and acetone. The culture of the aspirate showed heavy growth of β-hemolytic streptococci, group A.

The patient was admitted to hospital with the diagnosis of reaction to insect bite or arthropod envenomation and cellulitis. Administration of penicillin G, 2 million units given every four hours intravenously, was started. Treatment with steroids was begun, but discontinued because it had been started relatively late and because the cultures were positive. By the morning of the fifth day, an eschar measuring 4 cm by 6 cm had formed in the area of hemorrhage (see Figure 2). That night the eschar was debrided and approximately 20 ml of purulent material was collected. The dermis had been undermined and this was debrided.

The following morning the tremor was gone, and muscle and joint pain were remarkably improved. The lesion continued to expand. Three days later necrotic tissues were debrided down to the musculoaponeurotic tissues, exposing the Achilles tendon posteriorly. No tendons, nerves or vessels were damaged (see Figure 3). Motion of the right ankle improved shortly afterward.

Saline wet-to-dry dressings and sutilains ointment (Travase) were used to promote granulation and prevent accumulation of necrotic tissue. Sharp debridement was done as indicated.

Further undermining of the dermis for 2 to 3 cm beyond the edges of the skin was noted 23 days after presentation. These areas were debrided and Nu-Gauze wicks were placed. Shortly after, a split-thickness meshed skin graft and a protective plaster cast were applied. On examination one week later and six weeks after presentation, there was a complete take of the graft and a full range of motion of the foot and ankle (see Figure 4).

Discussion

There are at least ten different species of Loxosceles spiders in the United States. Six of them have been proved experimentally to cause necrotic arachnidism: Loxosceles reclusa, the first to be discussed in North American literature and the best studied[2] (see Figure 5); Loxosceles laeta, the common cause of necrotic arachnidism in South America; Loxosceles unicolor, first discovered in California and Arizona in 1969,[10] but reported as early as 1961 in Texas;[5] Loxosceles deserta,[10] subsequently found to have caused many cases in Southern California previously attributed to L. unicolor and Loxosceles arizonica;[11] and Loxosceles refescens.

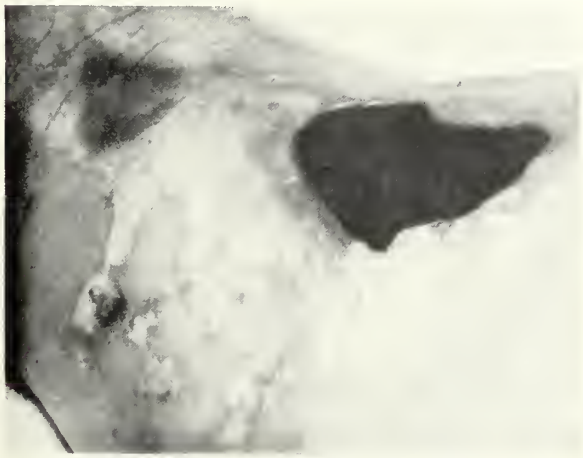

Figure 2.—Eschar formation 96 hours after initial symptoms.

Figure 3.—Final debriding before skin graft. Note extensive skin and fatty necroses. Muscle, tendon, major nerves and vessels were spared.

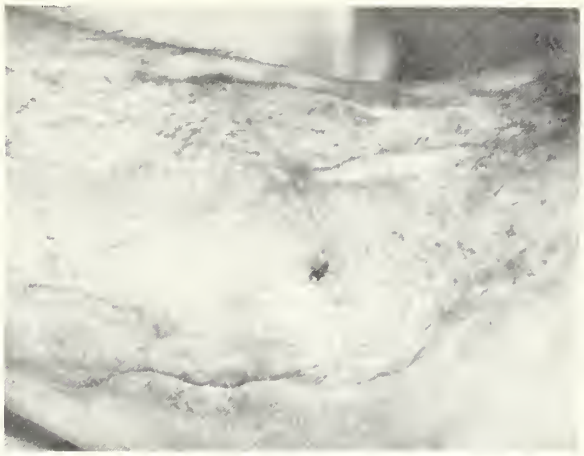

Figure 4.—Skin graft six months after original lesion began to form.

Loxosceles spiders have the same general body shape as black widow spiders. There is a typical violin marking over the septal thorax that accounts for the common name, violin spider. In some species this marking is so faint that it may easily be overlooked. These spiders vary in size from 6 to 20 mm, and in color from yellow to dark brown. Loxosceles species seem to prefer dark quiet places, often indoors—such as in undisturbed clothing, bedding, furniture and storage sheds. They are nocturnal feeders and run with amazing speed in the face of adversity, provided there is an avenue of escape. Unlike black widow spiders, both male and female Loxosceles spiders can cause serious envenomation.

The Venom

In addition to similarities in habitat, at least three—and probably more—of Loxosceles species have similar venom. Venom of Loxosceles spiders has been shown to contain many components, including collagenase, dipeptides, esterase, protease, deoxyribonuclease, ribonuclease, phospholipases and hyaluronidase.[12] Wright, Elgert and Campbell, however, could find only hyaluronidase

and esterase. They found that inactivation of hyaluronidase in the venom did not stop dermonecrosis.[13]

Later work by Elgert and co-workers showed that rabbits could be immunized against Loxosceles spiders by using increasing doses of venom. Antivenom produced in this way prevented dermonecrosis in animals injected with venom.[14] In a comparative study by immunodiffusion and electrophoresis of three Loxosceles species, antigenic similarity of the venom of each species was found.[15] This accounts for the fact that L. laeta antivenom decreases necrosis from bites of other Loxosceles species. Evidence shows that venom-complement interaction causes pronounced infiltration of polymorphonuclear leukocytes into surrounding tissues. In experimental animals made either neutropenic or hypocomplementemic, edema and necrosis did not develop at envenomation sites.[16] Lysis of polymorphonuclear leukocyte lysosomes that contain kinin-forming enzyme activity, mast cell rupturing activity and vasoactive cationic proteins, plus acid and neutral proteins, may account for a large part of the tissue damage (see Figure 6).

Figure 5.—Loxosceles reclusa spider.

In contrast to the well-studied mechanism of local necrosis, that of systemic hemolytic reactions remains unclear. Denny, Dillaha and Morgan found that venom alone had a hemolytic effect on human red cells *in vitro*. The hemolytic component in the venom was heat labile, but not complement dependent. Lecithin incubated with venom breaks into two components, which suggests that venom contains a lysolecithin that hemolyzes red cells.[17] Smith and Micks contradicted these findings. *In vitro* studies with extracts of venom, cephalothoraces and abdomens from Loxosceles resulted in complete hemolysis of red cells exposed to abdomen extract, partial hemolysis to extract of cephalothoraces and no hemolysis of red cells in contact with venom alone. The hemolytic process occurred at 37°C and was greatest with L. rufescens.[15] Variation in results of experiments relating to hemolysis may be due to different methods of preparing the extracts, contamination with saliva of mouth parts or by variation in mammalian red cell physiology.

Diagnosis and Treatment

In the case presented, there was a moderately severe reaction to the spider bite. Both humans

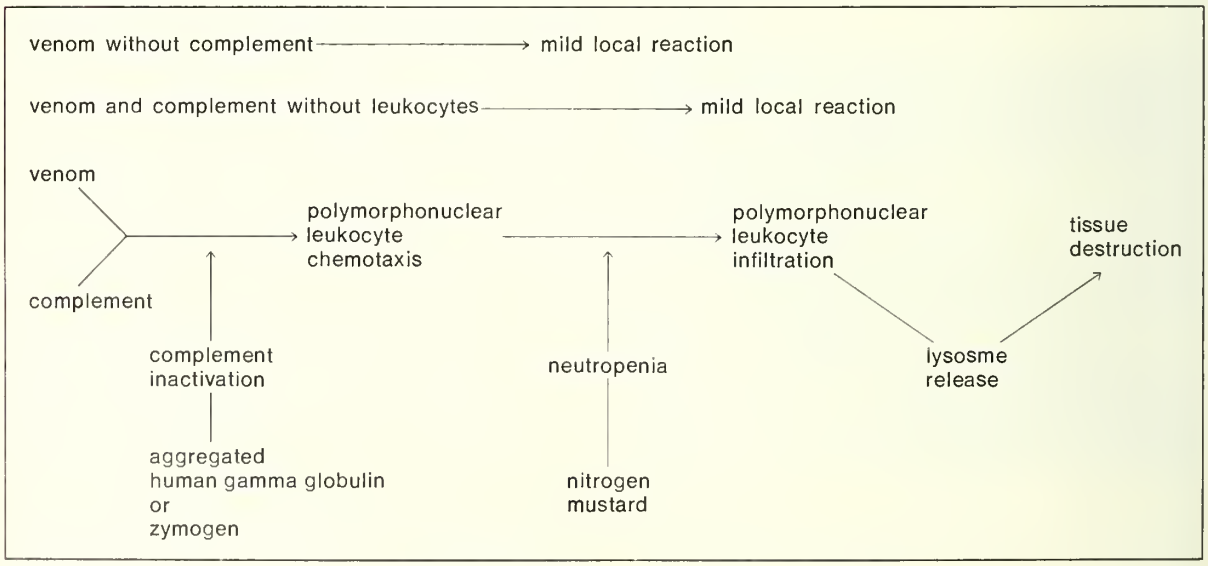

Figure 6.—Mechanism of injury.

and animals have the same general progression of symptoms, beginning with bleb formation and erythema at the site of the bite; followed by increasing pain, edema and erythema, and finally resulting in ischemia with blanching and eschar formation. Symptoms may, however, vary from negligible to fatal.

Early diagnosis and evaluation are necessary for proper treatment. Harves and Millikan note that severe bites are marked by bullae formation, pain and ischemia within the first six to eight hours. If these symptoms do not occur, treatment is probably unnecessary.[12] If no spider is found, necrotic archnidism should be considered a possible diagnosis when someone presents with a discrete bleb formation on an erythematous base and an inordinate amount of pain. Some physicians recommend immediate excision of such lesions down to and including the first fascial plane, but it is understandable that excision is often delayed, especially because proof—the spider—is seldom seen. Hershey and Aulenbacher recommend excision after the eschar has formed and note that erythematous tissues should not be excised.[18] Medical treatment may be helpful, pending excision of the eschar. Russell suggests immediate initiation of a high dose of steroids within the first eight hours after the bite.[19] Findings from studies in animals indicate that administration of steroids is not helpful.[20] However, it is tempting to think that steroid therapy would be efficacious in lesions that are primarily mediated by inflammatory processes. Dexamethasone, 4 mg administered intramuscularly every six hours, is suggested for acute phases.

The almost inevitable secondary infection should be treated appropriately. Culture of the lesion in the case discussed grew β-hemolytic streptococci, group A. Other authors have noted frequent infections with resistant and opportunistic organisms. These were related to the use of prophylactic antibiotics and to the debilitated condition of the patients.[18] Russell also recommends using an oxygen chamber made from a large plastic bag, tape and an oxygen-flow catheter (if no oxygen chambers are available). In addition, Russell advises cleaning the lesions three times a day with aluminum acetate solution and painting the lesions with triple dye after each cleansing. Others have obtained good results with enzymatic debridement, using fibrinolysin and combined bovine desoxyribonuclease ointment (Elase). Sutilains ointment (Travase) was used in the case reported here, and resulted in good formation of granulation tissue and maintenance of a nonnecrotic wound.

Most authors agree that surgical excision of the eschar is the definitive treatment. The earlier the lesion is excised, the sooner systemic as well as localized signs resolve. Usually, fever, joint and muscle pain, anorexia, and local edema and erythema improve notably shortly after excision. The usual course is destruction of a well-demarcated area of dermis and underlying fat, with sparing of muscular and neurovascular structures. After the area of skin is delineated, further necrosis of fat causes undermining around the skin margins. These areas must be carefully debrided. After the necrosis is arrested and a good bed of granulation tissue is formed, a skin graft should be applied.

Conclusion

Loxosceles spiders are expanding their range of habitation, and physicians in the states where these spiders used to be rare should become more aware of the problem. Symptoms that indicate that a Loxosceles bite may be severe include early bleb formation, pronounced erythema and pain occurring within six hours. The mechanism is not entirely clear, but apparently involves complement-activated tissue damage. Beginning treatment promptly—including the use of steroids, local wound care and surgical debridement—should decrease severity of the symptoms and improve the outcome.

REFERENCES

1. Caveness WA: Insect bite complicated by fever. Nashville J Med Surg 10:333, 1872
2. Atkins JA, Wingo CW, Sodeman WS: Probable cause of necrotic spider bite in the Midwest. Science 126:73, 1957
3. Berger RS: The unremarkable brown recluse spider bite. JAMA 225:1109, 1973
4. Nance WE: Hemolytic anemia in necrotic arachnidism. Am J Med 31:801, Nov 1961
5. James JA, Sellars WA, Austin OM, et al: (1961) Reactions following suspected spider bite. A form of loxoscelism? Am J Dis Child 170:300, Aug 1969
6. Olson C, Minton SA: Spider bites and hemolysis. Pediatrics 33:283-284, 1964
7. Parsons MA: The brown recluse spider fact, not furor. Ohio's Health 27-32, Apr 1970
8. Lewis MI, Regan JF: Necrotic arachnidism. Calif Med 105: 457-462, Dec 1966
9. Keegan HC: Venomous bites and stings in Mississippi. J Miss State Med Assoc 495-499, Dec 1972
10. Gertsch WJ, Russell FE: Short communication loxosceles deserta Gretsch. Toxicon 13:203-204, 1975
11. Russell FF, Waldron WG, Madon MG: Bites by the brown spiders Loxosceles unicolor and Loxosceles arizonica in California and Arizona. Toxicon 7:109, 1969
12. Harves AD, Millikan LE: Current concepts of therapy and pathophysiology in arthropod bites and stings—Part 1. Arthropods. Int Dermatol 14:543-562, Oct 1975
13. Wright RP, Elgert KD, Campbell BJ, et al: Hyaluronidase and esterase activities of the venom of the poisonous brown recluse spider. Arch Biochem Biophys 159:415-426, 1973
14. Smith W, Micks DW: A comparative study of three species of Loxosceles. Am J Trop Med Hyg 17:651-656, 1968
15. Smith CW, Micks DW: The role of polymorphonuclear leukocytes in the lesion caused by the venom of the brown spider, Loxosceles reclusa. Lab Invest 22:90-93, 1970
16. Elgert KD, Ross MA, Campbell BJ, et al: Immunological

studies of brown recluse spider venom. Infect Immunol 10:1412, Dec 1974
17. Denny WF, Dillaha CJ, Morgan PN: Hemotoxic effect of Loxosceles recluses venom: In vivo and in vitro studies. J Lab Clin Med 64:291-298, Aug 1964
18. Hershey FB, Aulenbacher CE: Surgical treatment of brown recluse bites. Ann Surg 170:300, Aug 1969
19. Russell FE, Wainschel J, Gertsch WJ: Bites of spiders and other arthropods. Curr Ther 864-867, 1974
20. Berger RS: A critical look at therapy for the brown recluse spider bite. Arch Dermatol 107:298, 1973

Refer to: Rubinstein JS: Deliberate abuse of diphenoxylate hydrochloride, a schedule V narcotic. West J Med 131: 148-150, Aug 1979

Deliberate Abuse of Diphenoxylate Hydrochloride, a Schedule V Narcotic

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DIPHENOXYLATE is a meperidine congener frequently prescribed in the treatment of diarrhea. The drug is available in both tablet and liquid form (Lomotil, Colonil); each tablet and each 5 ml dose of the liquid contains 2.5 mg of diphenoxylate hydrochloride and 0.025 mg of atropine sulfate. Diphenoxylate hydrochloride is a schedule V narcotic.[1]

The chemical structure of diphenoxylate hydrochloride is similar to that of meperidine,[2] and the drug carries many of the risks and hazards characteristic of the opiates. Mild side effects include drowsiness, rash, dizziness, depression and nausea. Treatment of overdose or individual hypersensitivity reaction is similar to that for meperidine or morphine intoxication. Prolonged monitoring of the patient is essential because, although there might be an initial response to narcotic antagonists, life-threatening respiratory depression may occur as late as 30 hours following ingestion.[2] Several cases of accidental overdose in children have been reported.[3]

As with other opiates, the drug also has a potential for abuse. Though at therapeutic ranges (20 mg of diphenoxylate hydrochloride per day or less, in divided doses) opioid effects do not occur, doses of 40 to 60 mg at a time have been shown capable of producing a morphine-like euphoria.[4] Morphine-like addiction is also theoretically possible following prolonged use of the drug at high doses.

Recently, I encountered a case of deliberate abuse of diphenoxylate hydrochloride, and ordered a computer search of the literature for further information. Considering the frequency with which this drug is prescribed, its schedule V rating, and the great demand among abusers for its opiate congeners, it was surprising to discover that deliberate abuse of diphenoxylate hydrochloride for its subjective effects has never been reported in the literature.

Report of a Case

A 32-year-old man came to the psychiatric outpatient clinic with complaints of anxiety and depression over his inability to carry out his duties satisfactorily at work.

The patient had a long history of drug abuse, including the intravenous abuse of heroin, and at age 24 had been admitted to hospital for what he described as an inadvertent overdose. Following this experience he became "more cautious" in his use of drugs, resolved to stop using heroin; the patient broke all contact with the *street scene,* but continued to abuse pills, in particular barbiturates, as well as prescription opiates such as pentazocine and propoxyphene. In addition, the patient related that he had, over the past year, begun to abuse diphenoxylate hydrochloride, taking large doses of the drug intermittently, but never more than once or twice a week for periods of up to several weeks at a time.

The patient's first experience with the drug had been with a prescription given to his wife by her doctor as prophylaxis before an intended trip abroad. He had found the bottle of pills and, not being familiar with the drug, had looked it up in the *Physicians' Desk Reference.* He had learned that it was an opiate and, in large doses, could produce opiate-like effects. The patient enjoyed the sensation, and then began taking the drug regularly. He found that most physicians would issue a prescription for diphenoxylate hydrochloride with little question when he complained of diarrhea, even when he would specifically request the drug by name. On several occasions he informed the physician that he was about to embark on an extended trip abroad, and received large supplies of the drug. The patient would ordinarily take 60 to 100 tablets for the desired

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effect, which he described as a euphoria qualitatively similar to that produced by other orally taken opiates. Concomitant ingestion of alcohol or other drugs seemed to result in potentiation of the effects.

On one occasion the patient shared a quantity of the drug with a friend who reported experiencing a similar *high*. The patient did not report having been bothered by any adverse atropinic side-effects at his usual dosage. The largest single amount he ever took was about 140 tablets; at this dosage he did experience pronounced dryness of the mouth, and woke up the following morning with nausea and a severe headache. Though his euphoria at the higher dosage was significantly enhanced, the patient says he ordinarily restricts his dosage of the drug for several reasons: (1) He is afraid of damaging his gastrointestinal tract, (2) he conscientiously wishes to avoid addiction and (3) the cost of the drug, even when purchased at a pharmacy (as opposed to the *street price*), is fairly expensive.

Discussion

That this drug is abused is not either astonishing or remarkable; any medication—no matter how ostensibly innocuous—carries with it the potential for abuse. What is remarkable is the ease with which this drug, a narcotic, is obtained, and the apparent willingness of many physicians to issue prescriptions to a patient with little or no question.

Many physicians seem unaware either of the opioid pharmacological structure of diphenoxylate hydrochloride or of its consequent potential for abuse and dependency. An informal survey I conducted among physicians at two academic centers seems to confirm this. Of 20 physicians interviewed (all of whom stated they prescribed the drug "at least occasionally," and some said they did so "often") only six were aware of the pharmacological structure of the medication and of its potential for abuse. Ironically, in our case report the patient apparently had made more assiduous use of the *Physicians' Desk Reference,* for his own purposes than had the prescribing physician.

The absence of previous case reports is puzzling. The patient's statement regarding the enthusiastic reaction of his friend to the drug suggests that his experience is neither idiosyncratic nor unique, though the patent's lack of contact with the *street scene* renders him incapable of accurately appraising the extent to which the drug is being abused. The relatively high cost of the medication, even when obtained through licit channels, as well as the fact that diphenoxylate hydrochloride even as a salt is virtually insoluble in water[5] and therefore cannot be abused parenterally, may be contributory. This by no means, however, obviates the possibility that deliberate abuse of the drug, though hitherto unreported, may be widespread. At present I am collecting and documenting a more extensive series of cases.

It has been stated that subtherapeutic amounts of atropine sulfate have been added to the compound to discourage deliberate overdosage[2] (p 1449) This contention seems to conflict, however, with experimental data. Doses of less than 2 mg of atropine are, in an adult, unlikely to produce any clinically significant dysphoric effects.[6] Therefore, even 60 tablets, which is a quantity significantly beyond that which is theoretically required to produce a morphine-like euphoria, would not contain a sufficient amount of atropine sulfate to disturb the patient sufficiently, presumably, to discourage deliberate overdosage. This is particularly true because many opiate abusers are characteristically willing to tolerate considerable amounts of distress to obtain their high, "paying the price" not only in physical discomfort, but often, ultimately, in the typical, erosive, downward-spiral of the addicts' life-style.

The case reported here raises a number of questions. Clearly, there is a need for a heightened level of awareness among physicians concerning the pharmacological nature of the substance and its potential hazards, including the possibility of deliberate abuse and of habituation. Certainly a greater index of suspicion should be exercised when prescribing this medication for patients with histories of drug abuse, those who specifically request the drug by name and especially those patients who express a desire for inordinately large quantities of the medication. In addition, one must question the clinical sagacity of prescribing a narcotic-containing compound for any patient with diarrhea before potentially less hazardous drugs have been given an adequate trial. There is, unquestionably, no paucity of nonnarcotic medications, many of proven efficacy as well as safety, available on the market today.

Summary

Diphenoxylate hydrochloride is a drug frequently prescribed in the treatment of diarrhea.

Though it is chemically related to meperidine, deliberate abuse or dependency on this drug has never been reported. A case is presented in which the patient had been using the drug regularly, in large doses, for its morphine-like euphoriant effects. He had been obtaining the drug easily from physicians, and a heightened level of awareness among doctors concerning the abuse potential of this drug should result in greater vigilance in prescribing it.

REFERENCES

1. Jaffe JH: Narcotic analgesics *In* Goodman LS, Gilman A (Eds): The Pharmacological Basis of Therapeutics. New York, The Macmillan Co, 1970, pp 237-275
2. Physicians' Desk Reference. Oradell, NJ, Medical Economics, 1977, p 1448
3. Marsh AR, Lammiman D: Lomotil—A dangerous drug. JR Nav Med Serv 60:149-150, Winter 1974
4. AMA Drug Evaluations. Acton, MA, Publishing Sciences Group, Inc, 1973, p 794
5. Fraser HF, Isbell H: Human pharmacology and addictiveness of ethyl 1-(3-cyano-3,3-phenylpropyl)-4-phenyl-4-piperidine carboxylate hydrochloride (R-1132, diphenoxylate). Bull Narcot 13: 29-43, 1961
6. Innes IR, Nickerson M: Drugs inhibiting the action of acetylcholine on structures innervated by postganglionic parasympathetic nerves (antimuscarinic or atropinic drugs), *In* Goodman LS, Gilman A (Eds): The Pharmacological Basis of Therapeutics. New York, The Macmillan Co, 1970 pp 524-547

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Epiglottitis in an Immunosuppressed Host

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EPIGLOTTITIS is an acute infection of the supraglottic larynx with a major risk of airway obstruction secondary to cellulitis and edema. Diagnosis is made by history and examination of the epiglottis by lateral neck x-ray study or, preferably, indirect mirror examination. Treatment consists of maintaining an airway, and administration of antibiotics, oxygenated mist and probably corticosteroids. This case presented unique therapeutic problems because of the underlying malignancy, impaired immune status, previous therapy and essentially irreversible coagulopathy.

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Report of a Case

In a 16-year-old girl with stage IV non-Hodgkin lymphoma in relapse despite multiple chemotherapy regimens, increasing sore throat, fever and dysphagia developed. The patient was admitted to hospital. After specimens for culture were obtained, treatment was started with cephalothin, gentamicin and carbenicillin because of the compromised immune status and possible sepsis.

Initial examination showed mild pharyngeal inflammation and enlarged, tender cervical nodes. Blood and urine cultures showed no growth and a throat culture showed normal flora and Candida albicans. A complete blood count at admission showed 600 leukocytes, a hematocrit reading of 22 percent and a platelet count of 13,000, with bleeding noted from venipuncture sites and the nose. After six units of platelet transfusion, the platelet count was 20,000, with continued bleeding.

Because a throat culture showed Candida, amphotericin was added to the regimen on the second hospital day. At this time the sore throat and dysphagia were worse, the patient was unable to swallow her saliva and mild airway obstruction was present. A lateral neck roentgenogram (Figure 1) was obtained and showed a typical enlarged epiglottis consistent with epiglottitis. Otolaryngologic consultation was obtained and examination showed a pale, swollen epiglottis with edema compromising the supraglottic airway. It was felt that neither an atraumatically placed endotracheal tube nor the most meticulous tracheostomy was a safe procedure because of thrombocytopenia refractory to treatment associated with bleeding. It was elected to begin administration of corticosteroids, 12 mg of dexamethasone (Decadron) given intravenously, followed by 4 mg every six hours. Within 12 hours the patient's condition was improved, and she was able to swallow her own saliva and some liquids. Eighteen hours later a repeat lateral neck roentgenogram showed no abnormalities (Figure 2). Two days later the patient had resumed a regular diet and the epiglottis was found to be normal on examination. She was discharged home 11 days after admission without sequelae.

Discussion

Epiglottitis is traditionally classified as an infectious disease of the larynx, but because of its morbidity and mortality it would be better to

Figure 1.—Lateral neck x-ray film showing edematous epiglottis and effacement of vallecula.

Figure 2.—Lateral neck x-ray film 18 hours after treatment, showing an almost normal epiglottis.

think of it as primarily an airway obstructive process in order to emphasize the most important aspects of its course. The disease occurs most often in young children, but also occurs in adolescents and adults. The clinical course is usually characterized in children by rapid progression from a mild upper respiratory infection to a state of severe toxicity and respiratory embarrassment.

The course from onset to severe respiratory obstruction can be as short as six hours. In adults, this progression may take longer because of a proportionately greater airway diameter and less reactive tissues.

Early in the course of the disease when the patient complains of only sore throat and fever, an unwary observer may see nothing on physical examination. If mirror laryngoscopy is not done, the correct diagnosis is not made and the patient may be sent home with the disorder having been diagnosed as viral upper respiratory infection. Usually, the child returns within 12 hours with respiratory distress and the correct diagnosis is made. It is important to emphasize that a lateral soft tissue x-ray study in a child with fever, sore throat and negative findings on examination of the throat (results would be positive if indirect laryngoscopy were carried out) will usually confirm the diagnosis of epiglottitis.

Findings late in the disease process include fever, dysphagia, drooling with inability to swallow, a barking cough and a muffled voice. Respirations are shallow and the patient assumes a position of maximal airway patency (sitting upright with neck and chin extended). Stridor may not be prominent because of the low volume of air being exchanged. Deterioration is marked by signs of increased heart rate and respiratory effort, irritability, cyanosis, fatigue and progressive airway obstruction.

Pathologically, the disease is a cellulitis of the supraglottic tissues, and the cause is most often a bacterial infection with Hemophilus influenza, although other bacteria have been cultured and viruses may be causative in some cases.[1]

Many physicians feel that this disease is a surgical emergency in young children, if not all patients, and a safe airway must be established before airway compromise progresses.[2] Considerable debate exists among various authors on the best method of establishing an airway—intubation or tracheostomy.[2-8] These authors do agree, however, that although medical therapy is important, establishment of an adequate airway is the primary concern. The role of steroids remains controversial because no double blind efficacy trials have been done.

Strome and Jaffe[9] have prepared a rational treatment approach to adult patients with this

disease who present without significant airway compromise. Their regimen includes treatment with ampicillin, corticosteroids and mist, with continuous monitoring for signs of deterioration. They emphasize the need for prompt establishment of a safe airway in patients not responding to treatment. They reported successfully treating eight of ten patients without the use of airway intervention. In the other two patients intubation was required. Hawkins[10] reviewed 17 cases in adults, 13 were successfully managed medically and four required tracheostomy.

Summary

A 16-year-old immunosuppressed patient presented with typical signs and symptoms of epiglottitis. Pronounced thrombocytopenia associated with bleeding prevented carrying out either a safe intubation or tracheostomy. The relation of the Candida albicans noted on throat culture to the epiglottitis is not known.

There was significant improvement in the patient's condition within several hours after dexamethasone and amphotericin were added to the treatment regimen. Because airway intervention was not required, the case falls into the category of a success of medical treatment in a patient with a compromised airway.

Conclusions

Epiglottitis is an acute infection of the supraglottic tissues with significant risk of airway obstruction. Treatment consists of antibiotics, oxygenated mist and probably corticosteroids. Vigilant airway monitoring and appropriate intervention are of paramount importance. An immunosuppressed patient with this disease presents special considerations: increased risk of infection, altered flora and thrombocytopenia with clinical coagulopathy modify standard therapeutic considerations.

REFERENCES

1. Gorfinkel HJ, Brown R, Kabins SA: Acute infectious epiglottitis in adults. Ann Intern Med 70:289-294, 1969

2. Bass J, Steele RW, Wiebe RA: Acute epiglottitis: A surgical emergency. JAMA 229:671-675, 1974

3. Fearon B, Cinnamond M: Tracheotomy in acute supraglottitis: The treatment of choice. Laryngology 81:879-883, 1977

4. John GK, Sullivan JL, Bishop LA: Acute epiglottitis. Arch Otolaryng 100:333-337, 1974

5. Weber ML, Desjardins R, Perreault G, et al: Acute epiglottitis in children—Treatment with nasotracheal intubation: Report of 14 consecutive cases. Pediatrics 57:152-155, 1976

6. Tos S: Nasotracheal intubation in acute epiglottitis. Arch Otolaryng 97:373-375, 1973

7. Milko DA, Marshak G, Striker TW: Nasotracheal intubation in the treatment of acute epiglottitis. Pediatrics 53:674-677, 1974

8. Schuller DE, Birck HG: The safety of intubation in croup and epiglottitis. Laryngology 83:33-45, 1975

9. Strome M, Jaffe B: Epiglottitis—Individualized management with steroids. Laryngology 84:821-928, 1974

10. Hawkins DB, Miller AH, Sachs GB, et al: Acute epiglottitis in adults. Laryngology 83:1211-1219, 1973

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Leukoerythroblastic Reaction in Still Disease in an Adult

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A LEUKOERYTHROBLASTIC REACTION is characterized by the presence of immature erythrocytic and neutrophilic precursors in the peripheral blood.[1] The presence of these immature cells usually suggests evidence of a structural or neoplastic problem of the bone marrow. Such conditions are thought to allow the premature release of marrow precursor cells into the peripheral circulation. We recently treated a young woman in whom the final diagnosis of adult Still disease* was made more complicated by the presence of a leukoerythroblastic reaction. This paper discusses the course and treatment of the disease in this patient. In addition, we review the hematologic manifestations of Still disease in adults.

Report of a Case

A 19-year-old Mexican-American woman presented to the Los Angeles County-University of Southern California Medical Center on November 1, 1977, with a one-day history of a painful, swollen right knee. She also said she had had fever, chills, myalgias and a sore throat for the previous five days. Three days before admission, the knee had become painful, hot and swollen but these symptoms resolved spontaneously. In addition, she noted that her fingers were tender and swollen.

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*The WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

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She gave no history of Raynaud phenomenon, conjunctivitis, skin rash, hair loss, chest pain, photosensitivity, mouth ulcerations, morning stiffness, weight loss or previous joint problems. Her last sexual contact was two weeks before admission. She had been treated for gonorrhea in 1974 and had had a therapeutic abortion in 1975. She reported no allergies.

On physical examination the woman appeared ill. Temperature on admission was 38°C (100.4°F). There was no adenopathy. The lungs were clear and the heart was normal. Neither the liver nor spleen was palpable and there were no abdominal masses. Pelvic examination showed a gravid uterus. Examination of the skin showed a few maculopapular eruptions around the anterior aspect of the upper chest. The right knee was erythematous and tender, and an effusion was present.

No abnormalities were shown on an x-ray study of the chest, and an electrocardiogram showed a sinus tachycardia. The hemoglobin was 10.1 grams per dl; hematocrit, 29 percent; platelets, 220,000 per μl; leukocyte count, 13,300 per μl with 60 percent neutrophils, 28 percent band forms, 7 percent lymphocytes, 4 percent monocytes and 1 percent metamyelocytes. The peripheral blood smear showed normal red cell morphology and typical Pelger-Huët nuclei in the mature neutrophils. The electrolyte and liver function studies were normal. The erythrocyte sedimentation rate was 62 mm per hour. The VDRL was nonreactive. The right knee was aspirated and 5 ml of serosanguineous fluid was removed. The cell count was 400 mononuclear cells and the glucose content 111 mg per dl. Cultures of the fluid were negative for bacteria including Neisseria gonorrhoeae, fungi and acid-fast bacilli. Throat, cervical and rectal cultures grew only mixed flora.

The patient was initially thought to have acute gonococcal arthritis and, therefore, therapy with high doses of penicillin was started. However, the low synovial fluid leukocyte count (repeated), negative cultures and persistent fever were not consistent with the diagnosis. Administration of penicillin was stopped, therefore, after five days. At the patient's request, a therapeutic abortion was carried out soon after admission.

On November 4 the patient's peripheral blood smear showed a leukoerythroblastic reaction. This was characterized by the presence of nucleated red blood cells (2 per 100 leukocytes) and immature neutrophilic precursors as early as the myeloblastic or, more commonly, the promyelocytic and myelocytic stages. There was no evidence of gastrointestinal bleeding nor had many laboratory tests been done before the onset of the reaction. Leukoerythroblastosis continued for 11 days (Figures 1 and 2). After this time, leukocytosis continued without nucleated red cells or leukocytes seen earlier than the myelocytic stage. The red cell morphology, platelet count and reticulocyte count remained normal throughout the patient's hospital stay.

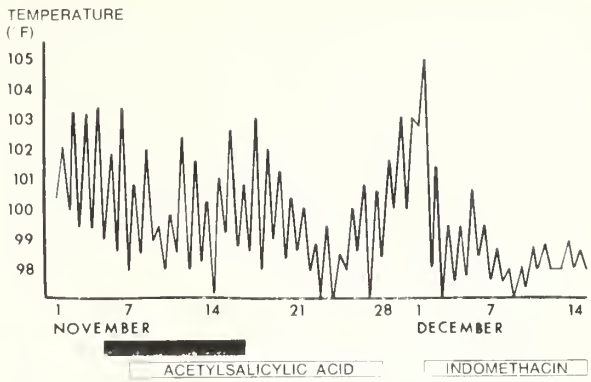

Figure 1.—The fever pattern of the patient during her hospital stay showing response to antipyretic therapy. Black bar denotes the 11-day period of leukoerythroblastosis. White bars indicate periods of drug therapy.

Seventeen blood cultures, including anaerobic cultures and two for Brucella (cultured on Castenadas media), were negative. Cultures of liver biopsy, bone marrow and cerebrospinal fluid specimens were also negative.

The antistreptolysin O titer was 85 Todd units, febrile agglutinins were negative and viral titers for rubella, adenovirus, herpes simplex, rubeola and cytomegalovirus were all compatible with previous infection. Latex fixation with rheumatoid factor and antinuclear, antideoxyribonucleic acid (anti-DNA), antideoxyribonucleoprotein (anti-DNP) and antimitochondrial antibody tests were all negative. The third component of complement was 85 mg per 100 ml initially but was 150 when repeated (normal, 100 to 200). Heterophil test and test for hepatitis B surface antigen were negative. The urine pregnancy test was positive. Serum protein electrophoresis and serum immunoelectrophoresis were normal. Direct and indirect Coombs tests were negative.

Barium swallow with small bowel follow-throughs and barium enema were normal. Computer-assisted tomographic (CAT) scan of the

abdomen and pelvis showed splenomegaly and normal retroperitoneal structures. Bone marrow aspiration and biopsy studies showed a hypercellular marrow with an increased myeloid:erythroid (M:E) ratio (Figure 3). No tumor, granuloma or fibrosis was found. Stainable iron was present. Skin tests with Purified Protein Derivative (PPD) of cocci and histoplasma antigens were negative but a test for mumps was positive.

Throughout her stay in hospital the patient was noted to have a rash. It was found first on admission, and by the eighth hospital day it was present as a maculopapular rash on both the arms and abdomen. The rash later became more generalized with patchy areas on the thighs, trunk, back and buttocks. It was occasionally pruritic and changed in location and appearance from day to day. After a month the rash disappeared leaving some areas of hyperpigmentation. Tender lymphadenopathy also developed during the patient's third week in hospital, most notably in the submandibular, cervical and inguinal areas. The size of the nodes (1 to 3 cm) varied from day to day. By the time of her discharge, she had only small, nontender, freely movable inguinal lymph nodes.

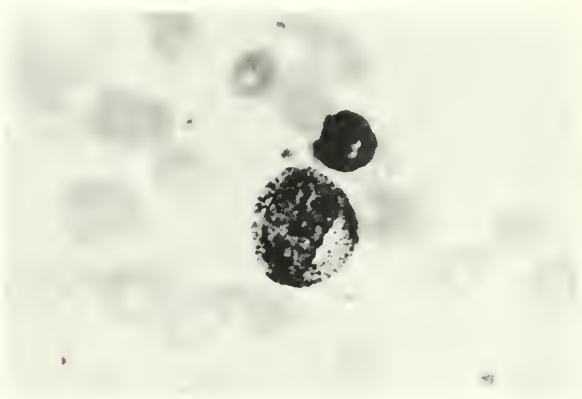

Figure 2.—High-power view of peripheral blood smear during period of leukoerythroblastosis. An early dysplastic myelocyte is shown with a nucleated red blood cell (reduced from ×320). (Photograph taken by Dr. Adelbert Cramer, Division of Hematopathology, LAC-USC Medical Center.)

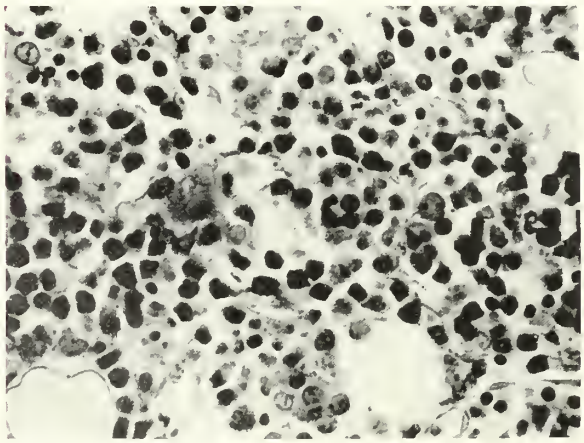

Figure 3.—Medium-power view of bone marrow biopsy specimen at time of the leukoerythroblastosis. There is an increased myeloid/erythroid ratio with a predominance of early granulocytic precursors (reduced from ×160). (Photograph taken by Dr. Adelbert Cramer, Division of Hematopathology, LAC-USC Medical Center.)

The patient's fever continued with single daily spikes as high as 40.6°C (105°F) through the first 32 days of her hospital stay despite intensive salicylate therapy (Figure 1). After completion of a workup a diagnosis of adult Still disease was made and a regimen of indomethacin was begun on December 1. This treatment resulted in a prompt defervescence after two days of therapy (Figure 1). She was discharged on December 14, and has had no recurrence of fever. She did have a transient knee effusion after she discontinued taking the indomethacin but this resolved promptly after reinstitution of the medicine. Her complete blood count returned to normal except for the persistence of the Pelger-Huët anomaly.

Discussion

Still disease in adults is characterized by the presence of high spiking fevers, a fairly typical macular skin rash, a fleeting arthritis and negative serologic tests for rheumatic disease.[2] In addition, pericarditis and ankylosing spondylitis may be seen in such cases, particularly in the cervical vertebrae.[2] This constellation of findings may also be found in other diseases such as rheumatic fever, erythema multiforme, the rheumatoid variants and in infectious diseases such as meningococcemia and gonococcemia.[3] Hence, the diagnosis of Still disease necessitates the exclusion of other diseases which may resemble it but whose causes are better defined. The diagnosis is also supported by the usually prompt response to antipyretic therapy and the subsequent relatively benign course.[2]

In addition to the protean systemic manifestations of Still disease that are present in many patients, there are some noteworthy hematologic findings. As in any chronic inflammatory process, a normochromic, normocytic anemia develops during the course of the disease. In one series Bujak and associates noted a mean hemoglobin of 9.6 grams per dl. This anemia remits during

the disease's asymptomatic periods and returns during its exacerbations.[4] In addition, the mean highest leukocyte count in the above series was 23,500 per μl with a range of 5,400 to 36,500. In eight of their patients there were counts greater than 18,000 per μl. This is also consistent with the observations of Schaller and Wedgwood.[5] In their study of 32 children with a systemic presentation of juvenile rheumatoid arthritis, they noted that in 29 of their 32 patients there were counts greater than 12,000 with some reaching levels of 75,000 per μl without concomitant infection.

The presence of a leukoerythroblastic reaction in the peripheral blood usually alerts physicians to the presence of either a primary bone marrow disease or a myelophthisic process due either to tumor or granuloma. Leukoerythroblastosis, therefore, has been regarded as having a dire prognosis because of the diseases with which it is associated. Recently, however, a large series of cases in which this reaction occurred has been summarized.[6] In a group of 215 patients with leukoerythroblastosis reported by Weick and coworkers, 136 had malignant diseases including hematologic and nonhematologic tumors and myeloproliferative disorders, 17 had hemolytic disease and 62 had a variety of other conditions, the most common of which was gastrointestinal bleeding. The authors pointed out that in this large series, although most had malignant diseases, 37 percent proved to have more benign disorders associated with leukoerythroblastosis in the peripheral blood. These other associations involved a variety of organ systems. Among the other cases were septicemia, myocardial infarction, connective tissue disease, chronic lung disease and inflammatory bowel disease.

The pathophysiology of a leukoerythroblastic reaction is not completely understood. It is thought that the release of normal cellular elements from the bone marrow into the peripheral blood requires an egress of cells through the marrow circulatory channels. This egress depends on the size of the aperture and the deformability of the cells that are maturing in the marrow.[7] It has been shown experimentally that the developing marrow precursors become more deformable as the maturation process from myeloblast to polymorphonuclear cell takes place.[7] In a true myelophthisic process, it seems likely that the bone marrow-peripheral blood barrier is disrupted, thereby allowing normally poorly deformable cells such as promyelocytes, myelocytes and nucleated red cells to leave the circulation prematurely. Despite this proposed mechanism, it is difficult to know how diseases which do not involve the marrow directly can lead to a similar premature release of cells such as occurred in this patients with Still disease.

The presence of leukoerythroblastosis combined with fever, splenomegaly and lymphadenopathy in this patient expanded the diagnostic considerations to include diseases either primary to or invasive of the bone marrow. No such conditions were found; the bone marrow showed only granulocytic hyperplasia. The response to therapy and subsequent course were also consistent with Still disease. The cause of the leukoerythroblastic reaction in this disease is unknown. The above review suggests, however, that this reaction in Still disease is uncommon.

Summary

We describe the case of a 19-year-old woman in whom adult Still disease was diagnosed. During the course of her illness a leukoerythroblastic reaction developed lasting 11 days. This was manifested by the presence of nucleated red cells and immature neutrophilic precursors as early as the myeloblast stage on the peripheral blood smear. The presence of this reaction caused us to search for other causes for her illness. None were found.

A review of the hematologic manifestations of Still disease suggests that although anemia and leukocytosis are common, leukoerythroblastosis is not mentioned. Leukoerythroblastic reactions occur most commonly in primary bone marrow diseases and in invasive diseases of bone marrow. A recent review suggests, however, that leukoerythroblastosis noted in the peripheral blood may occur in more benign disease processes. The diagnosis of adult Still disease in our patient appears to be an example of this more benign association.

REFERENCES

1. Vaughan JM: Leuco-erythroblastic anemia. J Pathol Bacteriol 42:541-564, 1936
2. Bywaters EL: Still's disease in the adult. Ann Rheum Dis 30:121-133, 1971
3. Gilliland B, Mannik M: Disorders of the joints and connective tissue, section 14, *In* Thorn G, Adams RA, Braundwald E, et al (Eds): Principles of Internal Medicine. New York, McGraw-Hill Book Company, 1977
4. Bujak JS, Aptekar RG, Decker JL, et al: Juvenile rheumatoid arthritis presenting in the adult as fever of unknown origin. Medicine 52:431-444, 1973
5. Schaller J, Wedgwood RJ: Juvenile rheumatoid arthritis: A review. Pediatrics 50:940-953, 1971
6. Weick JK Hagedorn AB, Linman JW: Leukoerythroblastosis. Mayo Clin Proc 49:110-113, 1974
7. Lichtman MA: Cellular deformability during maturation of the myeloblast: Possible role in marrow egress. N Engl J Med 283:943-948, 1970

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

The Safety of Agricultural Chemicals

To the Editor: The recent decision of the Environmental Protection Agency (EPA) to temporarily ban the use of the herbicide 2,4,5-T in forestry, but not in the food chain, is an issue of interest to the medical profession. The medical literature contains not a single case of intoxication nor of adverse effects occurring in the general public from the use of the phenoxy herbicide, 2,4,5-T. Nevertheless, the decision to ban 2,4,5-T was based upon the possibility of "imminent hazard" to human health and therefore the decision becomes a medical issue.

The use of this phenoxy herbicide has been argumentative since the Vietnam war when the military decided to use the chemical as a weapon. The philosophical issues of that decision remain part of the great debate concerning that war. The scientific issues of that decision stem mainly from the contaminant dioxin called TCDD, a known teratogen and suspected as a carcinogen and a mutagen.

Current uses of 2,4,5-T in agriculture came into sharp focus when a group of concerned women in Oregon suspected a temporal relationship between their miscarriages and the spraying of 2,4,5-T upon adjacent forestry land. The EPA sent in two investigative teams, the conclusion of the first being that there was no cause-and-effect relationship but the conclusion of the second study was that a temporal relationship was a possibility and the chemical was therefore banned. Now, because of shoddy data collection and questionable methodology in performing statistical analysis, the scientific credibility of the second phase of the EPA study is considered doubtful. In addition, the scientific credibility of a major governmental regulatory body, the Environmental Protection Agency, is also suspect—which may be even more unfortunate.

The time has come for all physicians, both those in clinical practice and those in public health, to involve themselves in the safety issues of agricultural chemicals in our society. If illnesses are occurring that result from the incidental exposure of the public, these illnesses should not only be reported but also documented. Studies need to be performed by members of our profession rather than by those people trained in a variety of other disciplines—as was the case with the second phase of the EPA study. Clinical investigation, cooperative with but independent of both industry and government, needs to be developed. Otherwise, further regulatory decisions of both public health and economic magnitude will result from superficial analyses such as has occurred with 2,4,5-T.

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The Plight of Tithonus

To the Editor: The other day, as I hurried through my nursing home rounds, my thoughts turned to Tithonus. As you recall, Tithonus was a happy young man who so loved life that he beseeched Aurora, goddess of morning, to grant him immortality. His wish was granted, but in making his pleas to Aurora he had failed to ask for perpetual youth, as well. And so, Tithonus lived on and on to become an old man who could not die.

Tennyson, in "Tithonus," one of his finest poems, eloquently describes the sorry state of the shriveled man who had lived out his time and who had "long passed beyond the goal of ordinance." In our depressing, proliferating geriatric wards there are dozens, no hundreds, of unfortunate aged who sit passively in the halls, a glazed, faraway look in their eyes, no doubt dreaming of "happy men that have the power to die."

As we physicians pass through the nursing home corridors, aware of the faint smell of urine and phenol, let us be reminded that, "but for the grace of God, there go I." A humbling thought, yet one that does let us greet each new day with gratitude.

Could it be that the goddess of morning grants us doctors a longer useful life so that we can continue to work and serve? Or are we given the reward of a longer life of service simply because we have deliberately chosen to remain productive? Every practicing physician has witnessed the rapid mental and physical deterioration of the early retiree, who, once out of the harness, slowly but surely becomes aware of his unworthiness.

In our society to be worth something is to be loved. Swiss geriatric apologist Paul Tournier, in speaking of the plight of the aged, wisely observed that "there is one essential, profound, underlying problem, and it is that the old are *not loved*. They do not feel themselves to be loved, and too many people treat them with indifference, and seek no contact with them."

The next time I walk the halls of a nursing home let me remember to stop a moment longer, to hold a gnarled hand, to put an arm around a shoulder, to let a little love for my elderly fellowman show through. Let me remember that this may be Tithonus, who is making his silent plea to Aurora, "Release me, and restore me to the ground!"

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Functional Overlay

To the Editor: Dr. Walter Bromberg's article on functional overlay (130:561-565, Jun 1979) was thoroughly enjoyable. He is an astute, reflective, scholarly and experienced psychiatrist. This was an exemplary specimen of first-class medical writing and I sincerely hope that our colleagues read it carefully for its form and manner of expression, as well as for its content. It sets a classic standard for couching cogent thinking in literarily creative and meaningful terms rather than resorting to buzz words, transiently stylish cliches and professional jargon.

Illness and injury are the lot of every living thing. The problems are not limited to negligence and compensation cases. Suffering is the name of our game and it is our job to discriminate between the degrees of anguish and how much is physical and what that does or does not do to the ego. But, if we are to fulfill our responsibility as specialists in medicine, we have to think and express ourselves in consequential terms that have a concrete meaning to another. Is this man sick or not? In what way is he suffering and is the suffering legitimate or not? Is it a put-on or not? If not, let us have the details as Dr. Bromberg so well describes them. But, a nonmedical rubric is really beneath our dignity.

The development of consultation liaison psychiatric services to medical and surgical departments of hospitals in the last generation or so has demonstrated a significant emotional aspect to physical illness. Curiously, no one serving these areas of medicine came up with a catch phrase like functional overlay. Of course, no money is involved in people's private suffering. Why is it that compensably injured persons suffer so much more chronically? Why are such persons operated on so much more frequently and repetitively? A hundred years ago, the German compensation system already had coined the term compensation neurosis, the grandfather of functional overlay and, like it, a nonpsychiatric diagnosis. Foster Kennedy, the noted neurologist at Bellevue 50 years ago, elaborated a detailed comparison between the postinjury clinical pictures of insured and noninsured persons. It illustrated the role of motivation graphically, but also showed the degree to which ordinary human cupidity can foster downright swindling. That very danger makes it incumbent upon psychiatrists to be totally incredulous and evaluate every possible aspect of the cases before them with a dispassionate degree of clinical rigor which should include every bit of objective evidence obtainable, as well as the self-serving complaints of the claimants. Regrettably, this is not always the case and psychiatry, too, is developing a snide public image because too many colleagues provide totally unsupported diagnoses, careless inquiry and transparently unprofessional findings. They are satisfied with the standard that accepts a nonthought like functional overlay. That kind of approach to a medical problem is costing society billions in wasted funds and incalculable degrees of social decay on a par with the financial greed characterizing other areas of our body politic.

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* * *

To the Editor: I concur strongly in Dr. Walter Bromberg's concept of "functional overlay" as a nondiagnosis. In fact it seems often to reflect a defensive need in the physician. Likewise the term malingering should be looked upon as a nondiagnosis. No matter how transparent the facade, one must assume that the patient would use some other coping method rather than pain complaint if

there were a more successful method known to said patient.

The patient described by Dr. Bromberg would be, by present standards, considered to have inappropriate treatment. One may be quite certain that none of the specialists mentioned "put a finger" on her problem. If this were done, she would have demonstrated muscle trigger point pain or cervical facet pain—most likely both. These people do have weakness of the hand. They are found to have minor to major defects in range of motion in the neck and all have an assortment of the common trigger points so well delineated by Travell, Bonica, Pace and others.[1-3]

The mere act of touching, identifying and explaining these pains as due to dysfunction puts patients in a different situation where they can involve themselves in their own recovery using exercise and strengthening procedures. Only by bridging the psychological and the physical, by responding to a patient's body language of pain with the body language of palpating, touching and accepting, will we as physicians avoid making casualties of patients such as the one described.

I must apologize for raising doubts. Having seen some 5,000 chronic pain patients over the last ten years, my experience tells me that someone should have put a finger—literally put a finger—on this problem.

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REFERENCES

1. Travell R, Rinzler, SH: The myofacsial genesis of pain. Postgrad Med 2:425-434, 1952
2. Bonica JJ: Management of myofascial pain syndromes in general practice. JAMA 164:732-738, 1957
3. Pace JB: Pain, pharmacology and treatment techniques. JCE Clin Med 86:31-40, 1979

Removal of Retained Gallstones

To the Editor: I read with interest the Specialty Conference[1] and accompanying editorial comments[2] concerning treatment of retained gallstones in the May 1979 issue. They were generally informative and current with one glaring exception. The Specialty Conference totally ignored and the editorial comment all but ignored the newest and most promising approach to patients with this problem—transduodenal endoscopic sphincterotomy. This technique is not "considered experimental" in the United States as stated by Dr. White but rather is established and in common practice in many referral centers throughout this country. Although it is currently being done on frail and elderly patients at increased risk from open laparotomy, endoscopic sphincterotomy is now achieving a high success rate (90 percent to 95 percent) and sufficiently low morbidity (5 percent to 8 percent) and mortality (1 percent) to be considered preferred treatment in all patients with retained common duct stones if T-tract removal is not feasible or achievable. In the past two years at the University of California, San Francisco, we have carried out 50 successful sphincterotomies in 54 attempts; the major barriers to success being abnormal anatomy of the distal bile duct or duodenum. We have had two complications: one, a moderate blood loss from the sphincterotomy incision requiring two units of blood, and the second a case of moderate postsphincterotomy pancreatitis that responded to conservative therapy. None of our patients have died nor have any required emergency operations. In this series we have done five successful sphincterotomies and stone extractions in patients in whom there had been unsuccessful attempts at stone retrieval via the T-tube tract. There is no doubt in my mind that endoscopic sphincterotomy is an established technique for retrieval of retained gallstones, at least at the University of California, San Francisco.

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REFERENCES

1. Longmire JP Jr, Goldstein LI, Sample WF, et al: The treatment of retained gallstones—Interdepartmental Clinic Conference, UCLA School of Medicine (Specialty Conference). West J Med 130:422-434, May 1979
2. White TT: Techniques in treatment of retained gallstones (Editorial Comment). West J Med 130:435-437, May 1979

* * *

Dr. Longmire Replies

To the Editor: Dr. Shapiro is indeed correct in pointing out the potential value of transduodenal endoscopic sphincterotomy as an additional approach to the removal of common duct stones. His enthusiastic presentation of a quite respectable, but still somewhat limited, experience with the procedure includes two of the most frequently encountered complications, postsphincterotomy bleeding and pancreatitis, and should be viewed in the perspective that surgeons have recognized for many years—that is, that a retrospective report of outstanding results from a certain technical procedure obtained by a particular group of experts may serve as a goal to be emulated, but can by no means be taken as indicative of the results to be expected in the country at large. The

exact role of the procedure in our armamentarium I believe most physicians feel is still to be defined. Currently, in the hands of a limited number of endoscopists in this country who are expert in this technique, endoscopic ..ansphincter stone removal has been useful. As experience with the technique increases, its indications as well as its hazards will be defined.

Incidentally, I might also take this opportunity to question the statement in Dr. White's editorial comment which accompanied our panel discussion. He assumed that if 600,000 cholecystectomies were carried out each year in the United States, there would be 30,000 patients left with retained stones rather than the 3,000 to 4,000 we had proposed.

According to the National Center for Health Statistics[1] there were 402,000 cholecystectomies done in the United States in 1974. The true incidence of retained stones following cholecystectomy is difficult to establish, and most of the figures available pertain to years during which operative cholangiograms were used infrequently and choledoscopy not at all, and many patients were operated upon late in the course of their disease when the incidence of stones in the common bile duct was increased.

Recent studies all show a pronounced decrease in the incidence of retained stones. Our estimate of the number of retained stones following cholecystectomy was based on the assumption that 20 percent of the 400,000 cholecystectomies would be accompanied by common bile duct exploration and that retained stones might occur in 3 percent to 5 percent of the patients so explored. Thus it would seem that our guess of 3,000 to 4,000 retained stones might be somewhat more realistic today than the 30,000 proposed by Dr. White.

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REFERENCE

1. Utilization of Short Stay Hospitals—Annual Summary for the US, National Center for Health Statistics. US Dept of Health, Education, and Welfare, 1974

Evidence in Medicine as a Natural Science

To the Editor: In medicine, nowadays, the rule of evidence for the acceptance of new knowledge of a concept, a therapeutic procedure or a medication for a specific ailment is the prospective double-blind randomized study (PDBRS). Historical controls, pilot studies, preliminary information and, even less, promising results smack of inconsistency and prematurity and therefore are looked at with a critical eye, a skeptical mind or at least, like the twist of the pretzel, they are to be taken with a grain of salt.

Speculation by an experimentalist is to be avoided as a forbidden path, as foregone or analogistic conclusions, beyond the probabilities of random sampling. It is rightfully so in the simple logic of common thought processes, for the roads of speculation (literally mirror-image, that is virtual, unreal) are paved with refractive potholes and parallactic false steps.

A fundamental difference exists, however, between speculating and theorizing, between speculation and theory. While speculating is extrapolating beyond the limits of the physical evidence, theorizing is actually experimenting with previous physical evidence not at the laboratory bench but in the laboratory of the mind.

For those so endowed it is possible to leap over and bridge across the same path of double-blind or foolproof experimentation and seize the evidence by the process of creative association. Their discoveries precede further experimentation rather than follow it. They anticipate by creative deduction rather than discover through experiment. So it was, as good examples, for Einstein and for Harvey as for Medawar and Burnet. Yet their evidence is only accepted after experimental confirmation; this is not as much for the sake of the discoverer (for, as Guy, once so confronted, only said "but I already knew it") as it is for the sake of those who can only accept it as an experimental fact.

The advent of direct observation by Galileo and the experimental method by Claude Bernard in natural sciences has brought down to larger numbers of prepared persons the ability to gather scientific evidence (hence called scientists) much as serial industrial manufacturing provided to the masses products that before were only available to the privileged wealthy.

But because the experimenter so contributes to the vastness of scientific discoveries, it must not be overlooked that today, and henceforth, he will overlap with true theoreticians. These must be distinguished from the quickstep observer since no one has yet invented an "inferometer." The experimenter is forever uncertain, the theoretician knows. The experimenter is analytical, he has to deal with all the uncertainties and variables

of the parameters and measurements of the system he sets in motion and draw tentatively the fleeting evidence from it. The theoretician is a synthesizer, evidence comes to him with a certainty that, though Heisenbergian, is only limited by the dimensions and forms of the universe within which he is working. Euclid is right on his two to three dimensions as Einstein is on four or five, and so on. The Euclidean view was necessary but not sufficient. Where Euclid felt secure in the simple beauty and *superficial* logic of planar geometry, Einstein foresaw the limitations of even his generalized relativity and searched continuously for further unification.

A distinction must be made between unproved experimental observation, often erroneously called theory, and *theoria vera,* the result of veridical and integral observations by the mind. The example given of Medawar and Burnet illustrates the many that could be quoted of advances in biology and medicine by experimenting in the mind. Tyler, for instance, predicted that backgrafted F_1 hybrids would develop lymphomas. As basic data of first order become available from partial and limited syntheses of function-structure phenomenology, the minds of the real theoreticians will transduce and translate them into higher, and yet simpler, forms of synthesis-comprehending.

There is no precision and exactness in scientific evidence. Its median, focal, photographic clarity, like the insisting thematic leitmotiv of a Beethoven symphony or the immediacy of a Flemish portrait, are no more true (or more beautiful) than the indistinctness of impressionistic painting and music and even distorting and less tonal followers. All are part of a Poisson curve, a Dalton-Gaussian distribution, nature's trials and errors, a quantum, discontinued nature, all wave-matter, time-space. Only the human mind is able to integrate it into abstract thought of continuity. The experimental observations close in a polyhedron whereas the theoretical thought finishes it to a sphere.

In medicine, with its inherent pragmatism, we go by what works, what time tests and sanctions, what gets wide acceptance, what is well remembered and even fashionable. In narrower circles one even speaks of standards of community practice. PDBRS are relatively recent and exist only for a very limited number of concepts, procedures and medications. Medicine cannot stop to take a total PDBRS inventory of its knowledge stock. Such inventory would be irrelevant because the precision of its discoveries lies not in whether they are PDBRS-proof but in the concatenation of factual data, that is, in their cross-veracity. This cross-veracity is what appears as a sudden, thrilling, illuminating evidence and inner, unconfessed, certainty to its discoverer and less, sometimes never, to its critics (even the constructive ones), until it is *released* once again in another equaled mind.

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A Technique to Prevent Headaches After Diagnostic Lumbar Puncture

TO THE EDITOR: Lumbar punctures for diagnostic examination of cerebrospinal fluid (CSF) have been carried out since the turn of the century and have frequently been accompanied by post-lumbar-puncture headaches (PLPH).[1]

Tourtellotte[2] has reported in his summary of 21,000 standard lumbar punctures that the incidence of PLPH is 32 percent for diagnostic lumbar punctures, 18 percent for obstetrical spinal anesthesia and 13 percent for nonobstetrical anesthesia. The typical PLPH[2] starts about 10 hours after the lumbar puncture with a backache, followed within 14 hours by a postdural headache. The range of onset is from 15 minutes to four days after the procedure. It persists for 2 to 14 days (average 3 days) and is characterized by a retro-orbital frontal aching and pounding. Occasionally, it is accompanied by nausea and vertigo. Immediate relief usually occurs when the person lies down. Few people are able to carry out normal activities with such a headache and analgesics are of little use. The most effective treatment is the epidural blood patch recently reviewed in this journal by Brodsky.[3] Of 570 patients with PLPH, 95 percent had relief after this procedure. Many patients are subjected to risk of PLPH, since more than 800,000 lumbar puncture trays are used each year in nonfederal and non-state-operated hospitals (unpublished data provided by IMS-America, Ambler, Pennsylvania 19002, 1978).

Although the PLPH can be effectively treated, it is preferable to prevent them from occurring. In most instances this can be done by using a thinner needle than is standard. The single factor that contributes most to the development of PLPH is the diameter of the hole made in the dura by the needle.[2,4] The use of the prone position for 1 to 24 hours following the procedure to prevent

PLPH is standard practice, although its utility is open to question and is inconvenient for outpatients. A small needle for lumbar puncture was discussed by Hoyt in 1922,[5] but has been mentioned only a few times in the literature.[2,6,7] Standard diagnostic lumbar puncture trays utilize 18- to 22-gauge needles, making it inconvenient to carry out the procedure with thinner needles.

Chemical analysis of cerebrospinal fluid may have increasing use for assessment of cerebrospinal fluid chemicals and their relationship to a number of neuropsychiatric disorders. The use of small needles to obtain specimens of fluid for chemical assay is warranted when cerebrospinal fluid pressure is not needed; small needles cannot accurately be used to assess pressure.

The present successful technique to minimize PLPH has been adapted from Green[6] and has been found to be easy to do and is adaptable to current disposable trays. The patient is placed in the usual lateral decubitus position. A local anesthetic is injected at the third or four lumbar space to a depth of 1 to 1.5 cm. A 1½ inch, 20-gauge needle is then placed into the skin and directed as if it were a lumbar puncture needle (that is, aimed toward the umbilicus). It is inserted 1½ inches in large persons and 1 inch in thin persons. This needle is necessary since the thin spinal needles will not easily penetrate skin. A 25- or 26-gauge spinal needle is then inserted bevel up through the intradermal needle and through the dura. Inserting the needle bevel up minimizes the number of longitudinal dural fibers that are cut. A *pop* may or may not be felt as the dura is penetrated. When the stylet is removed, cerebrospinal fluid will appear within five to ten seconds. The fluid will flow slowly under normal pressure and therefore a small length of the plastic tubing that comes in the tray is attached to the needle hub, a syringe is attached to the free end of the tube and fluid is slowly withdrawn at a rate of not greater than 1 ml per minute. More rapid withdrawal may produce a headache like that of PLPH. Between 20 and 30 ml of fluid may be obtained without difficulty in this manner. After sufficient cerebrospinal fluid has been obtained, the inner and then the outer needles are withdrawn and patients then roll to the prone position for one hour. They then can carry out normal, nonstrenuous daily activities. An hour of bedrest is not necessary and has been deleted without untoward sequelae in outpatient situations.

If the dura is not apparently entered, the inner needle must be withdrawn before repositioning the outer needle which should be partially or completely withdrawn and redirected and the attempt repeated. If this fails repeatedly at more than one interspace after the patient has been *carefully* and *symmetrically* positioned, a larger single spinal needle may be used successfully. In our hands, this is necessary less than 5 percent of the time and constitutes the only drawback of the procedure.

We have recently carried out lumbar punctures for diagnostic and research purposes in 36 normal persons and 60 inpatients with psychiatric disorders. Ages ranged from 17 to 69 years old. In 15 of the normal persons probenecid lumbar puncture was also done.[8] Written informed consent was obtained from each subject. All lumbar punctures were done with the described technique and were atraumatic. Patients were followed by telephone or by personal interview over the ensuing week to determine the occurrence of PLPH. No PLPH occurred after any of the 96 initial procedures. One would have anticipated between 20 to 30 of these would have been followed by PLPH. In four of the normal persons PLPH developed within eight hours after a probenecid lumbar puncture, done 40 hours after the first procedure. Two of these subjects had engaged in strenuous physical activity following the lumbar puncture and associated this with the onset of the PLPH. The increased incidence following these PLPH's may have been due to the presence of a second hole in the dura.

In settings where cerebrospinal fluid is needed for chemical or hematological analysis, anesthesia or outpatient use, use of a small needle may be a preferable technique due to the decreased incidence of PLPH.

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REFERENCES

1. Jones RJ: The role of recumbency in the prevention and treatment of postspinal headache. Anesth Analg 53:788-796, Sep-Oct 1974
2. Tourtellotte WW, Haerer AF, Heller GL, et al: Postlumbar Puncture Headaches. Springfield, IL, Charles C Thomas, 1964
3. Brodsky JB: Epidural blood patch. West J Med 129:85-87, Jul 1978
4. Tourtellotte WW, Henderson WG, Tucker RD, et al: A randomized, double-blind clinical trial comparing the 22 versus 26 gauge needle in the production of the post-lumbar puncture syndrome in normal individuals. Headache 12:73-78, Jul 1972
5. Hoyt R: Apparatus for withdrawing spinal fluid without post-puncture reaction. JAMA 78:428-429, Feb 1922
6. Greene BA: A 26 gauge lumbar puncture needle: Its value in the prophylaxis of headache following spinal analgesia for vaginal delivery. Anesthesiology 11:464-469, Jul 1950
7. Myers L, Rosenberg M: The use of the 26 gauge spinal needle. Anesth Analg 41:509-515, Jul-Aug 1962
8. Goodwin FK, Post RM, Dunner DL, et al: Cerebrospinal fluid amine metabolites in affective illness: The probenecid technique. Am J Psychiatry 130:73-79, Jan 1973

Refer to: Harer WB Jr: Tel-Med—A success story (In the Forefront). West J Med 131:162-164, Aug 1979

Tel-Med—A Success Story

W. BENSON HARER, JR., MD, *San Bernardino, California*

Providing health information by telephone with tape-recorded messages has spread from a local medical society project to a nationwide information resource. More than 800,000 calls per month are received in 180 cities, accessing a library of more than 300 subjects.

TEL-MED—a program to make taped health information available by telephone—was begun by the San Bernardino County (California) Medical Society in March 1972.[1] Started as a local experiment to improve public access to accurate medical information, the concept has been expanded into a major resource available to more than 65,000,000 people through sponsoring agencies in 180 cities.

Tel-Med is now a nonprofit, tax exempt educational corporation which administers the program nationally. All tapes in every city must have the approval of the local county medical society. This insures conformance with local standards and assures acceptance. The multiple levels of review also assure that information is accurate, up-to-date and clearly presented.

The tape library now addresses more than 300 subjects in English, with 200 of those also available in idiomatic Spanish. The length of the recordings varies from three to six minutes. Members of the San Bernardino County Medical Society have written most of the scripts, but many have also come from physicians in other Tel-Med cities. The scripts are edited and revised by Tel-Med staff into simple language for comprehension at the level of an eighth grade education. A panel of physicians reviews the revisions for accuracy and quality of presentation. The final script is professionally narrated and recorded on the type of tape cartridges used by the radio broadcasting industry.

People desiring access to information dial the local Tel-Med telephone number and request the tape by name or number. The local Tel-Med operator selects the proper cartridge from a bank of tapes and plugs it into a slot in a sophisticated playback device (see Figure 1). At the conclusion of the message, an electronic signal automatically disconnects the line and ejects the cartridge, which is loaded with the tape in a continuous loop so that it is immediately ready to play again.

In a recent nationwide survey,[2] practicing physicians indicated by a two-to-one margin that they felt "medicine has already done about all it can to reduce mortality and that henceforth attention should shift to prevention. . . ." When asked which single preventive program could promote health the most, and therefore should receive top government priority, 53 percent said public education.

Because Tel-Med programs meet these needs by emphasizing maintenance of health and prevention or early detection of disease, public response throughout the nation is consistently enthusiastic and supportive. As a bonus, the sponsoring agencies have reaped a harvest of good will and favorable publicity—a rarity in these

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Reprint requests to: W. Benson Harer, Jr., MD, 1800 North Western Avenue, Suite 101, San Bernardino, CA 92411.

Figure 1.—A Tel-Med switchboard operator answers a request for one of the 300 English and 200 Spanish tapes in the Tel-Med library.

times when physicians, hospitals and medical organizations are often on the defensive. By properly informing the public, Tel-Med guides them to proper utilization of available facilities. The taped messages effectively supplement physician and staff counseling for patients and their families. An easily accessible link of communication between providers and consumers has resulted. Any suggestion of propaganda or commercialism is scrupulously avoided.

Because callers remain anonymous, they can request vital information on sensitive subjects such as venereal disease or birth control without fear. Accurate information is presented on drug abuse and locations where help is available. A frightened, insecure or unsophisticated listener can seek assistance with confidence and without embarrassment about his ignorance or the nature of his concern.

Tel-Med is definitely cost effective. A careful analysis has been conducted of the Tel-Med program in Pittsburgh (the study has not yet been published). From inception in June 1976 through February 1978, total expenditures were $113,996. In this period there were more than 500,000 calls for Tel-Med tapes by about 125,000 consumers. This amounts to less than 23 cents per call. There is no less expensive means to provide specific requested health information.

A survey was also conducted of 522 Pittsburgh telephone subscribers. It showed that 41 percent had heard of the Tel-Med program and about 15 percent had used it. Those who had used the program reported 92 percent satisfaction with the information provided. They also reported positive changes in behavior and more appropriate physician referral for problems. Of course, the effectiveness of achieving the latter goals is difficult to assess quantitatively; however, it has been the consistent experience of sponsoring agencies from feedback in their communities that tapes do successfully transmit desired information.

TABLE 1.—*Most Requested Tapes*

1. Marijuana
2. Masturbation
3. Am I Really Pregnant?
4. Vasectomy
5. Gonorrhea
6. Tommy Gets His Tonsils Out
7. Syphilis
8. Venereal Disease
9. Breast Cancer
10. LSD
11. Teen Years—The Age of Rebellion
12. I'm Just Tired, Doctor
13. Vaginitis
14. The Rhythm Method
15. You May Have Diabetes And Not Know It

While the range of subjects covered is very broad, the subjects which were originally identified as being in most demand have consistently ranked among those most requested nationwide. These subjects reflect major social concerns—venereal disease, birth control and drug abuse (Table 1).

The pilot program was funded by grants of $24,500 from Regional Medical Programs Area VI, $10,500 from the California Medical Education and Research Foundation (CMERF) and $11,000 from the San Bernardino County Medical Society. With termination of the Regional Medical Programs in 1974, a one-year grant of $150,000 was provided by the Department of Health, Education, and Welfare to permit transition to a self-sustaining basis capable of propagation across the country. An additional grant of $45,000 from the American Medical Association Education and Research Foundation made it possible to develop a companion program, Tel-Hospital, that provides specific information for hospital patients about tests and procedures. This latter program is now in operation in two cities.

Tel-Med is now financially solvent and self-supporting through the modest charges made for the library and its maintenance in licensed agencies throughout the nation.

Tel-Med, Inc. is paid $20 per tape to develop the initial library. The total library of tapes is then maintained at a cost of $30 per month regardless of the number of tapes. Newly revised,

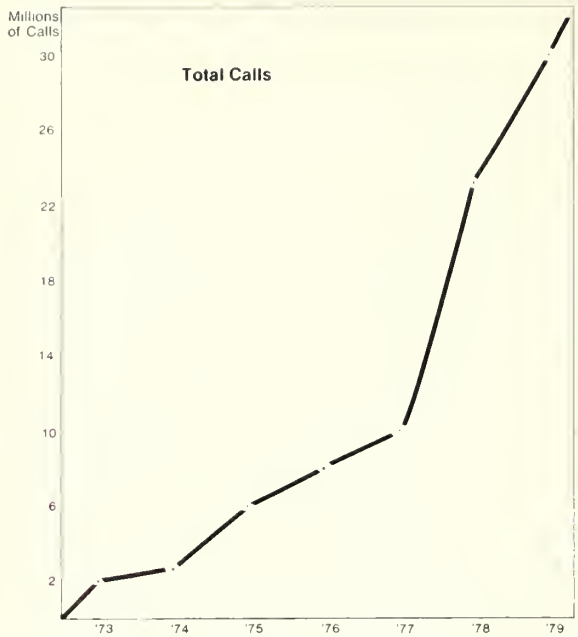

Figure 2.—Graph showing total number of calls for Tel-Med health information tape-recorded messages nationwide since the program's inception in 1972.

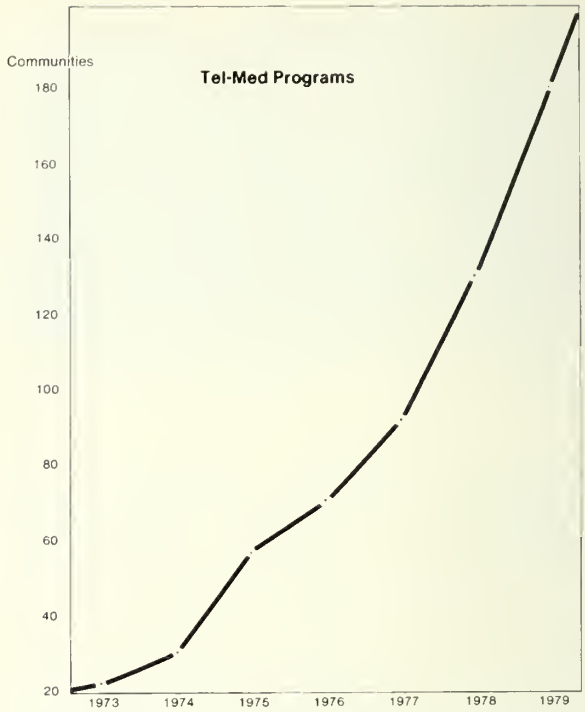

Figure 3.—Graph showing number of communities that have established Tel-Med services since the initial project was started by the San Bernardino County Medical Society in 1972.

updated tapes are provided at a cost of $9.75.

Growth has been steady since the program first spread to San Diego and then across the country. The Indiana State Medical Association established a WATS line service to provide access to everyone in the state. In February 1978, Tel-Med was made available to 85 percent of the population of New Jersey through the simultaneous opening of 17 centers in that state.

A noteworthy by-product in this time of strained relations between the medical and legal professions has been the development of the companion Tel-Law program by the San Bernardino County Bar Association. They share the use and expense of the San Bernardino Tel-Med switchboard, and attorneys' wives alternate with those of physicians in staffing it.

The progress of Tel-Med validates the concept and the effort it has taken to implement it. Nationwide requests exceed 800,000 a month, with a total of 30 million since April 1972 (Figure 2). It seems clear that Tel-Med is in a phase of geometric expansion (Figure 3) and, obviously, a saturation point will be reached eventually. It does not seem unrealistic, however, to hope that within the next six years Tel-Med tapes will be available toll free to most Americans.

REFERENCES

1. Harer WB Jr: Tel-Med—A public medical information service by phone (In the Forefront). Calif Med 117:68-70, Aug 1972

2. Physicians favor shift to prevention—especially through education. Med World News 62, May 1978

Refer to: Stapleton TR: Mania in criminal populations (Information). West J Med 131:165, Aug 1979

Information

Mania in Criminal Populations

THOMAS R. STAPLETON, MD
Reno, Nevada

IN THE EARLY PART of this century, manic depressive disease was thought to be an important factor leading to the crime of murder.[1] With the passage of time, it has come to be recognized that manic depressive persons are much more dangerous when depressed than when they are in the manic phase. For example, in Bulgaria, between 1925 and 1965, there were 25 murderers who were felt to be suffering from manic depressive disease. Of those, 21 were in a depressed phase at the time of the murder. These murders were generally of the "altruistic" kind, in which the murderer felt that he was doing his victim a favor.

More recently, in 1976, a survey at the King County Jail in Seattle found that 7 percent of the inmates referred for psychiatric evaluation were suffering from mania.[2] During an 11-month period at the Lake's Crossing Center for the Mentally Disordered Offender in Reno, the forensic facility serving the entire state of Nevada, it was noted that five of 54 admissions were diagnosed as acutely manic and the diagnoses were subsequently supported by response to lithium. This 9 percent figure is strikingly different from the general population and strikingly similar to the findings in the county jail population in Seattle.

The incidence of manic depressive disease in the general population is said to be approximately three to four per thousand. The fact that the incidence of acute mania in persons being admitted to a forensic facility is 22 times higher than this incidence in the general population suggests an important role of manic disease in the antisocial behavior of these persons, forcing them into the criminal justice system.

In five patients who were diagnosed as acutely manic at Lake's Crossing there was remarkable uniformity in their stories and in their experience within the criminal justice system. They were all accused of relatively minor crimes involving no personal injury or serious property damage. The charges were uniformly related to failures in judgment and problems with excessive intrusiveness, which could certainly be considered characteristic of manic behavior. As an example, one man was talking to a store clerk about buying a gun and decided to take the gun outside the store so he could point it at things. There was no attempt to steal the gun, nor was there any threat to use the gun against other persons, just a failure to observe the rule that one does not walk out of a store carrying new merchandise which has not been purchased. All five persons were men, ranging in age from 24 to 58 years. They all responded to administration of lithium and were discharged from the criminal justice system by virtue of having their charges dropped as soon as their psychiatric disorder was under control.

The thrust of this information would seem to be that manic persons are very likely to fall into trouble with the criminal justice system because of their high level of intrusiveness and poor social judgment. It also appears that a manic person does not usually commit serious crimes and that he will be released by the criminal justice system when he is successfully treated. This seems to indicate that a manic depressive person is at some slight risk of committing serious crimes when in a depressed phase and at fairly high risk of falling into conflict with the criminal justice system because of trivial offenses during the manic phase. It suggests that populations of criminal offenders are likely to be highly enriched with respect to acute manic persons, and that early and proper diagnosis of these persons can facilitate their disposition within the criminal justice systems.

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REFERENCES

1. Schipkowensky N: Affective disorders: Cyclo-phrenia and murder. Int Psychiatr Clin 5:59-75, 1968

2. Petrich J: Rate of psychiatric morbidity in a metropolitan jail population. Am J Psychiatry 133:1439-1444, Dec 1976

Refer to: Pepitone-Rockwell F, Rosenblatt R, Corkill G: Pain clinic model for community practice (Information). West J Med 131:166-170, Aug 1979

Information

Pain Clinic Model for Community Practice

FRAN PEPITONE-ROCKWELL, PhD
RICHARD ROSENBLATT, MD
GUY CORKILL, MD
Sacramento, California

THE EFFECTIVE MANAGEMENT of chronic, benign pain remains a problem despite recent advances in explaining its pathophysiology. Because narcotics and other modalities of pain control are often ineffective, the therapeutic resources available to physicians are limited. Pain clinics staffed by teams of physicians and other health professionals have been established to provide a wider range of patient care expertise. This multidisciplinary concept was conceived by John Bonica,[1] an anesthesiologist who recognized the limited resources and effectiveness of solo practitioners attempting to manage complex pain problems. Bonica's multidisciplinary team approach included professionals from the following medical and surgical specialities: psychiatry, psychology, physical medicine, clinical pharmacology and family practice. Although proposed in 1953, this concept has taken hold only in the last ten years, with numerous pain clinics now active nationwide.

Originally, pain clinics were primarily hospital based and most emphasized care of inpatients. In contrast, the pain clinic at the University of California, Davis, School of Medicine was planned from its inception in 1975 to offer consultative services only. The clinic, using the multidisciplinary approach, tailored its program to meet the specialized needs of the medical community, and to operate with the limited existing resources. Patients were evaluated by the clinic team members and then referred back to their primary care physicians with a comprehensive recommendation for treatment. Treatment was provided at the University Medical Center only when it could not be obtained at the community level to minimize the cost of the program. Although currently operating in a university medical setting, this pain clinic is applicable as a model for a community pain clinic. This paper outlines the functioning of the University of California, Davis, School of Medicine pain clinic and, using statistical data collated over the preceding four years, projects the types of pain problems that can be anticipated at the community level.

Goals of the Pain Clinic

The implicit goal of every pain clinic is to eliminate suffering by patients with chronic pain. In many instances, this objective cannot be fully achieved. The operational objectives, whether explicitly stated or not, are as follows:

- Identify those patients whose source of pain (usually organic) can be identified and treated conventionally.
- Identify those patients whose source of pain is known but unamenable to current therapy.
- Identify those patients whose pain has neither an identifiable cause nor definitive treatment.

The latter two groups make up most of the patients in any pain clinic population and these patients, while least amenable to treatment, are frequently the abusers of medical resources: physician time, unnecessary admissions to hospital and needless operations and overuse of multiple drugs. At the very least, pain clinics can protect these patients from the high-cost, high-risk, intensive medical and surgical environment. Treating these patients conservatively, prescribing only medications that are necessary and counseling against further surgical procedures is both economically advantageous and humanitarian.

Patients often come to a pain clinic ostensibly to make the simplistic demand for relief from their pain. Yet, chronic pain patients as a group are notorious for having covert objectives. Alleviation of their pain, in many instances, is not one of their goals. Sternbach[2] has written extensively on this process, categorizing it as a variant of gamesmanship. In fact, many chronic pain pa-

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tients derive an almost perverse delight in highlighting the physician's inability to relieve their pain. Any practitioner involved in pain management should be thoroughly acquainted with the dynamics of these gamelike interactions.

A primary care physician often refers a chronic pain patient for improved care or because he or she is either overwhelmed or intimidated by this patient. A person with complex pain problems can physically and emotionally drain the solitary physician who is treating him or her. Therefore, education and support of referring physicians have become additional goals of the pain clinic.

Evaluation of the Chronic Pain Patient

Chronic pain problems present a complex interaction of organic, social and psychological processes. By the time a patient is referred to a pain clinic, a purely neuroanatomical approach to diagnosing the cause of pain will probably fail. Hence, in evaluating a chronic pain problem, most pain clinics pursue a comprehensive physical and psychological work-up of the patient. Our current diagnostic profile includes the following items:

- A letter from the referring physician.
- Pertinent old records and diagnostic studies.
- Completion of the Minnesota Multiphasic Personality Inventory (MMPI) by both patient and spouse.
- Composition of a one-day pain diary.
- An account of "my pain" by the patient.
- A comprehensive list of all medications with respective dosage schedules.
- Completion of a standardized pain questionnaire.
- A general medical examination.
- Pertinent medical and surgical specialty examinations.
- A psychiatric consultation.
- A home visit and evaluation by a social worker.
- A drug screen of urine and blood specimens.
- Appropriate laboratory tests (for example, x-ray films, electromyogram, bone scan, estimated sedimentation rate).

The unique aspects of the pain clinic evaluation, other than physicians' consultations and associated diagnostic studies, are the pain diary, questionnaire and social worker's home visit. The pain diary is intended to provide the pain clinic members with a detailed chronologic description of the patient's pain written at the time of its occurrence. The psychological interdependence of pain and the patient's environment is often shown in the pain diary. Difficulties arise in accurately describing pain; as a result, pain questionnaires have been developed by several investigators to try to categorize, using standardized terminology, the type and degree of pain. The pain questionnaire currently used in the University of California, Davis, School of Medicine pain clinic was developed by Dr. Prithvi Raj, from the Texas Neurological Institute, and has proved satisfactory.

The home visit by the social worker is very important because chronic pain in a family member can profoundly affect a home environment, resulting in psychopathologic responses by the spouse and occasionally the patient's progeny. The home visit documents these changes and is of major importance in developing a treatment plan.

Our experience has been that the nature and cause of the pain is rarely established by means of diagnostic studies. However, several occult neoplasms have been disclosed on bone scans, undiagnosed neuropathies are sometimes noted by the electromyogram (secondary to alcoholism, diabetes, and heavy metal poisoning) and analgesic abuse is routinely observed on urine drug screens. Nevertheless, the overall success rate of diagnostic studies in finding the cause of pain compared with that of conventional tests in finding the cause of organic disease is poor.

The pain clinic evaluation is intended to be a thorough, comprehensive review of the patient's problem. An administrative assistant coordinates the data collection because the patient's case is reviewed only on completion of the prerequisites. It is essential that the patient, the spouse and clinic members be present and comprehensive current reports completed on the day of the clinic evaluation. The chronic pain patient is interviewed by clinic members who then interview the patient's spouse. Often a totally different description of the patient's pain is given by the spouse. The treatment plan is developed by the team members after assimilating the patient's data and information from the interviews. Finally, the patient and spouse together are informed of the conclusions and the prospective treatment plan is discussed with them. A member of the clinic

notifies the referring physician of the findings and proposed treatment plan, and a letter summarizing the plan is sent.

Treatment Regimens for Chronic Pain Patients

Chronic pain management protocols are as varied as the patients, and each must be tailored to meet individual needs. Nevertheless, there are common elements.

Related Conventional Management

If a definitive treatment for the patient's pain exists, it should be used initially (for instance, carbamazepine therapy for trigeminal neuralgia or excision of stump neuroma for amputee pain).

Analgesic Medications

Patients requiring analgesics should be maintained on a drug regimen appropriate for their pain. Mild to moderate pain can normally be alleviated by nonnarcotic analgesics and severe pain best managed by methadone. Selection of a drug with a low potential for habituation and abuse is essential. Commonly prescribed analgesics such as Dilaudid (hydromorphone hydrochloride) and Percodan (a combination of oxycodone, acetylsalicylic acid, phenacetin and caffeine) are clearly contraindicated and simplicity of prescription is sought. Where possible, a three-level prescribing practice is used: acetylsalicylic acid for mild pain, codeine for moderate pain and methadone for severe pain. Clearly, this should be modified on occasion but it is a basic guideline for analgesic therapy.

Detoxification

Abuse of analgesics and sedatives is common among chronic pain patients. In our experience, multidrug dependence is best managed with in-hospital detoxification; the risks of withdrawal are minimized and long-term compliance improved. Detoxification should be managed only by experienced physicians because significant potential risks are involved.

Emotional Support

Because psychic alterations are the norm in persons suffering from chronic pain, behavioral change is an essential part of their treatment. Depression, with its many manifestations, is most commonly observed. Psychotropic medications, psychotherapy and group counseling have been tried with varying degrees of success. Newer modes of behavioral change (hypnosis and biofeedback) are also proving effective. Combining several of these modalities appears to be the treatment of choice.

Transcutaneous Stimulation

A new and exceedingly useful tool for managing chronic pain is the transcutaneous electrical stimulator. This wallet-sized device delivers electrical impulses to the body noninvasively to stimulate components of the nervous system, which results in local analgesia. Although its efficacy varies substantially depending on the type, location and severity of the pain, this strategy has the advantage of being innocuous and may be prescribed with confidence early in any form of chronic pain management.

Physical Therapy

For many patients deterioration in physical status accompanies chronic pain. Often, it is the patient's physical condition, not the pain, that prevents him or her from resuming a normal life. Therefore, physical therapy is an integral part of the treatment plan.

Occupational Disability and Rehabilitation Counseling

Occupational disability is another common accompaniment to many chronic pain syndromes. Most chronic pain patients eventually learn to adapt to their pain, but many are unable to return to their original jobs. With occupational counseling and vocational rehabilitation, many of these unemployed persons can resume work.

Many patients do not desire an invalid's lifestyle. Rehabilitation counseling can provide patients, particularly the young, with the opportunity or face-saving rationale they need in order to change—and this is sometimes welcome.

Social Service Counseling

Chronic pain in a family member can be very destructive to a marriage and the home environment. Supportive family counseling is indicated and is often beneficial.

We have briefly outlined the clinic's approach to treatment of chronic pain. But our limited knowledge of the nature, variety and pathophysiology of chronic pain prevents us from implementing a standard treatment protocol. Recent recognition of the role of endorphins in emo-

TABLE 1.—*Demographic Data of Pain Patients: 1976-1978*

	Women	*Men*	*Total*
Number of Patients	47 (56.6%)	36 (43.4%)	83 (100.0%)
Age (years)			
Range	18-84	21-74	
Mean	44.8	44.3	
	Number (percent)	*Number (percent)*	*Number (percent)*
Marital Status			
Married	33 (70.2)	32 (88.9)	65 (78.3)
Divorced	4 (8.5)	0	4 (4.8)
Widowed	4 (8.5)	0	4 (4.8)
Single	4 (8.5)	4 (11.1)	8 (9.6)
Unknown	2 (4.3)	0	2 (2.4)
Type of Pain			
Low Back	14 (29.8)	20 (55.6)	34 (41.0)
Chest	6 (12.8)	1 (2.7)	7 (8.4)
Other (limb, hip, etc)	27 (57.4)	15 (41.6)	42 (50.6)

tional status and pain transmission may point the way to more effective treatment of this common malady.

Funding of a Pain Clinic

The newness of pain clinics with their unconventional programs has impeded reimbursement, a predicament exacerbated by the expense of the mutidisciplinary team approach. Many private insurance carriers, unfamiliar with this multidisciplinary concept, have challenged pain clinics as bona fide providers of health service and have refused payment. Governmental health programs aggravate matters further by requiring supplemental reports and then rarely reimbursing the full charge. Often, a pain patient is unable to pay, being unemployed and having already exhausted his or her insurance coverage. All of these factors complicate billing and collection. Accordingly, the University of California, Davis, pain clinic uses a single, all-inclusive fee (exclusive of laboratory tests), rather than pursuing individual, fee-for-service billing by the participants of the pain clinic. This has substantially reduced the paper work involved, and reimbursement rates have improved as third party carriers have become familiar with the fee profile.

Operating Experience

Since 1976 the pain clinic at the University of California, Davis, School of Medicine has evaluated 83 chronic pain patients. This apparently limited number is deceptive because of the long

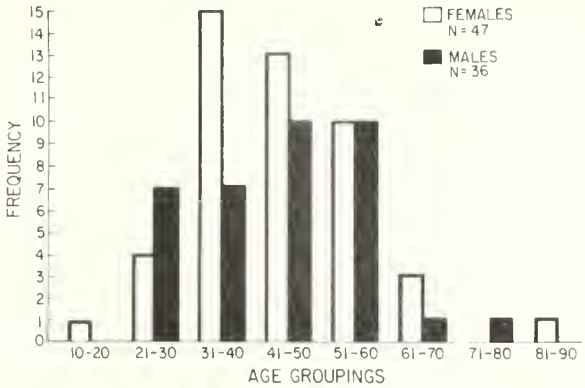

Figure 1.—Age distribution of pain clinic patients.

and arduous task of developing community referrals. At present, a waiting list in excess of 50 patients exists with referrals threatening to exceed the capabilities of the clinic. This is a very common problem for pain clinics and is indicative of the incidence of chronic pain problems. Of the 83 patients evaluated, 47 (56.5 percent) were women and 36 (43.4 percent) were men (Table 1). This is in contrast to the 2:1 female to male ratio noted in community general practices and in the frequency of hospital admissions, and may reflect the higher number of men with occupational injuries. Ages ranged from 18 to 84 years with nearly identical median ages for men and women (Figure 1). The incidence of chronic pain is not limited to middle age—both young and old are affected. The relative infrequency of referred cases of chronic pain in young and old may reflect pediatricians' and gerontologists' (geriatricians') unfamiliarity with the diagnosis.

Most of the chronic pain patients in this clinic population were married. The rate of divorce, anticipated to be high due to the stress on the home environment, proved unusually low. This was the case regardless of whether the chronic pain patient was a man or woman. In fact, none of our male patients were divorced. The incidence of chronic pain among single or widowed patients was proportional to their numbers in the overall population.

The anatomic distribution of pain in this clinic population reflects the preponderance of back pain in society. The incidence rate of head and back pain was second, followed by pain in the chest and the extremities. The specialty profiles (Table 2) of the referring physicians reflect the anatomic distribution of the pain. Neurologists, neurosurgeons and orthopedists referred approxi-

TABLE 2.—*Physicians Referring Patients to Pain Clinic: 1976-1978*

Specialties	*Number (83)*	*Percent*
General Practice	23	27.7
Neurology	16	19.3
Orthopedics	9	10.8
Neurosurgery	8	9.6
Family Practice	5	6.0
Physical Medicine and Rehabilitation	5	6.0
Internal Medicine	3	3.6
Psychiatry	2	2.4
General Psychiatry	2	2.4
Dermatology	1	1.2
Obstetrics-Gynecology	1	1.2
Anesthesiology	1	1.2
Hematology	1	1.2
Department of Rehabilitation	1	1.2
Unknown	5	6.0
Location		
Community Based	55	66.3
University of California, Davis, School of Medicine	24	28.9
Unknown	4	4.8

mately 40 percent of the patients, and 35 percent were referred by primary care physicians. It is of interest that most of these latter patients had been seen earlier by a neurologist, neurosurgeon or orthopedist. The remaining patients were referred by various other specialties. Two thirds of the patients seen in the pain clinic were not university patients, attesting to the success in attracting community referrals. A cursory study of types of pain and the specialty of the referring physician indicates no significant differences between university and community patients. Therefore, the statistical data presented can be construed as fairly representative of the variety of problems a community pain clinic can anticipate.

Summary

Drug abuse, psychiatric premorbidity and a complex interaction of social and psychological factors affect the treatment of chronic pain. A physician's frustration and resentment regarding a chronic pain patient's needs and skillful manipulation by the patient further complicate management.

The multidisciplinary team approach to the management of chronic pain has much to offer: advice against unnecessary surgical procedures; counseling; detoxification; the conservative use of medication; supportive psychiatric, physical or occupational therapies, and retraining to resume a normal life.

Fiscal viability is difficult to achieve for such a pain clinic unless care is taken to adjust patient mix, obtain prepayment to some extent and obtain commitment for preferential charging for facilities.

Fundamental to the successful functioning of a pain clinic is the dedication, availability and patience of the clinic coordinator, the one member of the staff who should be employed full time in the program.

REFERENCES

1. Bonica JJ: General clinical considerations, *In* Bonica JJ, Procacci CA, Pagni CA (Eds): Recent Advances on Pain. Springfield, IL, Charles C Thomas, 1974, pp 274-298

2. Sternbach RA: Pain Patients, New York, Academic Press, 1974, pp 52-78

ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *Members of the Editorial Board on occasion call attention to articles they consider to be important in other journals. These titles together with a brief assessment of the articles are published for the information of our readers.*

Presplenectomy Transcatheter Occlusion of the Splenic Artery

Levy JM, Wasserman P, Pitha N

Archives of Surgery
114:198-199, Feb 1979

DISCIPLINES: Surgery, Radiology

READABILITY: Good

The use of vascular occlusive coils induces embolization of the splenic artery to facilitate splenectomy.

—ROBERT B. ENGLE, MD
Orange, CA

"Steroid-Phobia" in Asthmatic Management

Tuft L

Annals of Allergy
42:152-158, Mar 1979

DISCIPLINES: All physicians concerned with asthma, other diseases relieved by steroids

READABILITY: Good to excellent

An interesting discussion by a pioneer allergist of the use of corticosteroids for many years with minimal or no side-effects. The deliberate use of the term steroid phobia is apt and the author's experiences in the use of corticosteroids constantly for more than 20 years on the same patients make interesting reading.

—NORMAN SHURE, MD
Los Angeles

Revised Radiologic Concepts of the Barrett Esophagus

Robbins AH, Vincent ME, Saini M, et al

Gastrointestinal Radiology (Berlin)
3:377-381, Oct. 1, 1978

DISCIPLINES: Internal Medicine, Gastroenterology, Surgery

READABILITY: Good

The Barrett, or columnar-lined, esophagus is almost assuredly a more common lesion than most of us recognize in view of the frequency with which we have seen cases. The authors have seen 39 patients with this entity, many without the high esophageal stricture previously considered a classical finding.

—H. JOACHIM BURHENNE, MD
Vancouver, BC

Causes and Mechanisms in Psychosomatic Phenomena

Wolf S, Goodell H

Journal of Human Stress
5:9-18, Mar 1979

DISCIPLINES: Psychiatry, Internal Medicine, Surgery, Dermatology, All subspecialties

READABILITY: Very good

A well-written article by highly qualified authorities clarifies the still too frequently confused and misunderstood basis of psychosomatic medicine by explaining that "visceral mechanisms of all sorts are connected with and are potentially responsive to electrochemical neural circuits in the brain that interpret life experiences."

—HELEN TAUSEND, MD
Los Angeles

A Multicentered Study of Lysine Therapy in Herpes Simplex Infection

Griffith RS, Norins LA, Kagen C

Dermatologica
156:257-267, 1978

DISCIPLINES: All physicians interested in herpes simplex (herpes complex) infection

READABILITY: Excellent

The authors describe a safe treatment for recurrent herpes simplex and expound rationale for its presumed effectiveness. At the very least this treatment is a splendid placebo. L-Lysine tablets, 312 mg, are available from the General Nutrition Corporation and the dose is three tablets a day for six months, then 1½ tablets a day for six months.

—REES B. REES, MD
San Francisco

International Symposium on Legionnaire's Disease

Balows A, Frazer DW

Annals of Internal Medicine
90:491-703, Apr 1979

DISCIPLINES: Internal Medicine, Family Practice, Infectious Diseases, Pulmonary Diseases

READABILITY: Very good

An exhaustive but splendid compendium of information on this important new entity in medicine. The single most important paper for primary care physicians is entitled "Clinical Aspects" and appears on pages 492-495.

—ROGER K. LARSON, MD
Fresno, CA

Percutaneous Decompression of Benign and Malignant Biliary Obstruction

Pollock TW, Ring ER, Oleaga JA, et al

Archives of Surgery
114:148-151, Feb 1979

DISCIPLINES: Surgery, Radiology, Internal Medicine

READABILITY: Very good

Bile ducts are opacified via skinny needle. A 16-gauge needle with polyethylene sheath is then introduced under fluoroscopic guidance. Subsequent guidewire and pigtail catheter introduction permits decompression and relief of jaundice. Catheter may be left indwelling for long-term palliation, or surgical therapy may be carried out after relief of jaundice.

—ROBERT B. ENGLE, MD
Orange, CA

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

CORONARY HEART DISEASE IN YOUNG WOMEN—Edited by M. F. Oliver, MD, FRCP, FRCPE, FFCM, FACC(Hon), Professor, Departments of Medicine and Cardiology, The Royal Infirmary, Edinburgh. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 262 pages, $23.50.

It has been known for many years that acute myocardial infarction is very uncommon in women under the age of 40 or 45, with the male/female ratio being approximately 10:1 in this age group. Women lose their advantage after menopause, especially as they approach 70 years old. Oliver, who for years has been interested in this strange epidemiological fact, has organized a symposium consisting of a large number of distinguished contributors largely from the United Kingdom to review the present knowledge on the subject. The date and place of the symposium are not given, but the fact that a good many of the references are from 1977 suggests that the symposium was held recently.

The participants in the symposium cover a wide variety of disciplines so that the material in the book brings together data and opinions not readily found in textbooks on cardiology. Endocrinologists, hematologists, epidemiologists, cardiologists, immunologists, experts in metabolic disease, pathologists and geneticists are all included and discuss the subject of coronary disease in young women from their particular vantage point. No discussion was provided regarding social-psychological-economic "stress" factors in etiology. An interesting omission from the distinguished group of participants is the absence of a psychiatrist or a psychologist.

The various possible mechanisms for the decreased prevalence of acute myocardial infarction in young women is discussed from a wide variety of approaches. There are considerable data on the role of the sex hormones during the course of the reproductive life of women, as well as after intervention by the various contraceptive pills and by estrogens after menopause. There is a comprehensive discussion of the role of metabolic and coagulation factors, especially following the use of oral contraceptives, and there is a discussion of the possible adverse effect of the androgens in men. The possible role of progesterones is discussed but not in the same detail as the estrogens. Spain raised the provocative question of whether the decreased prevalence was due to a protective effect of femaleness or an adverse effect of maleness. It is of interest that high density lipoprotein levels are higher in women than in men.

Each chapter is followed by a valuable, selected, up-to-date reference list and a short discussion by other participants which will be very helpful to the reader.

The book brings together all the current theories regarding coronary disease in women but does not conclude with a clear consensus as to the cause of the apparent protection in young females to acute myocardial infarction. Cigarette smoking has more than doubled during the last 25 years in women, especially young women, while consumption has leveled off in men during this period. The role of established risk factors such as hypertension, hypercholesterolemia, diabetes, a positive family history and cigarette smoking are all explored, especially when they occur in combination with metabolic and thrombotic factors that are important in women who take oral contraceptive agents. It was suggested that the adverse effects of oral contraceptive agents might be idiosyncratic, involving only a small group of women who are especially susceptible to their effects. Surgical menopause before the age of 40, especially when it occurs in association with other risk factors, is the most potent precursor of early coronary disease in women. It is clear that more research is required to elucidate the pathogenetic mechanisms.

There was a good deal of discussion about the safety and effectiveness of the dose of estrogens in the various contraceptive pills, whether 100, 50 or 30 μg. Insufficient data, however, were avaiable to indicate the advantages of the 30 μg pill with respect to its effect on blood pressure, lipids or coagulation factors. Further, the problem of "breakthrough" vaginal bleeding was not sufficiently explored.

The book should be of considerable interest to students of coronary disease, especially the discussion of coagulation and endocrine responses not usually elaborated in any detail in textbooks on cardiology. The book can be recommended to all physicians who wish an up-to-date account of the present status of the apparent "protection" of young women to acute myocardial infarction as well as an analysis of the increased incidence of the condition in women over 45 in the past 25 years. The experts in the different fields of medicine by examining in detail our current knowledge provide a distinct service to the profession.

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University of California, San Francisco
San Francisco

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GENERAL UROLOGY—Ninth Edition—Donald R. Smith, MD, Professor of Surgery and Chief, Section of Urology, College of Medicine and Dentistry of New Jersey, Rutgers Medical School, Piscataway, NJ; Recent Consultant in Urology, Egypt, under the auspices of People-to-People Health Foundation, Inc. (Project HOPE); and Professor of Urology, Emeritus, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1978. 541 pages, $14.50.

This ninth edition of a tried and true textbook about general urology is an update and expansion from the 1975 eighth edition. It has increased in size by almost 50 pages and in price by $3.50. It is well worth the investment for any serious student of urology. Dr. Donald Smith, who was formerly Professor and Chief of Urology at the University of California, San Francisco, has put together in this multiauthored paperback edition an excellent basic text. I tell our medical students that if they know everything that is in it, they will know more than most urologists.

Paricularly interesting and updated are the chapters on ultrasonic examination of the urinary tract and radioisotope kidney studies. The chapter on abnormalities of sexual differentiation is unusually well done, and infertility and vasectomy are well covered.

The chapter on chronic renal failure and dialysis, which formerly included transplantation, has been broken into two separate chapters with a rewrite of the two subjects. Particularly important and well done, it seems to me, is Smith's chapter on psychosomatic aspects of urology which he correctly puts into proper perspective. He includes a section on impotence in that chapter.

The paperback volume is lithographed and contains numerous, very informative, clear line drawings, photo-

graphs of x-ray films, some photographs of equipment, and graphs.

The work is extremely useful and comprehensive. It is the favorite textbook for our residents and medical students at the University of California, Los Angeles.

WILLARD E. GOODWIN, MD
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UCLA School of Medicine
Los Angeles

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THE PARENTS' MEDICAL MANUAL—Glenn Austin, MD, pediatrician in private practice, Los Altos, CA; with Julia Stone Oliver and John C. Richards. Prentice-Hall, Inc., Publishers, Englewood Cliffs, NJ (07632), 1978. 426 pages, $15.95 (Cloth), $8.95 (Paperback).

Glenn Austin, with a wealth of experience in pediatric practice, with two collaborators and an amazing 400 contributors has produced a most helpful and dependable book for parents. Parents should be encouraged to consult this book for many of their problems and responsibilities with their children and to use it as a ready reference.

Dogmatic opinions have been avoided and in many instances contrary views are presented so that parents can decide upon their own point of view.

There is a definite effort to avoid medical jargon—to the extent possible for a medical author. Parents will understand a great deal of the substance of the information and be able to profit. Many such books seem to overshoot the comprehension of many parents. Even those who do not read the book from cover to cover will be able to use it for ready reference.

Dr. Austin urges that pediatric advice should be provided before the birth of the infant, which is sound practice. (He might have counseled about the matter of "routine circumcision.") There are no gross deficiencies—I looked in vain for some reference to masturbation, thought to be so dreadful in some earlier times which parents may remember, although the newspaper columns now are most reassuring on this subject.

I could not agree with each of 400 opinions but the author emphasizes that there are contrary views. (I would not condone repeated smallpox vaccination for genital herpes!)

Physicians can profit from reading this book to help their own advice to parents.

EDWARD B. SHAW, MD
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University of California, San Francisco
San Francisco

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THE PARENTS' GUIDE TO CHILD RAISING—Editor: Glenn Austin, MD, pediatrician in private practice, Los Altos, California; Associate Editors: Julia Stone Oliver and John C. Richards, MD. Prentice-Hall, Inc., Englewood Cliffs, NJ (07632), 1978. 374 pages, $15.95 (Hardcover), $7.95 (Soft cover).

This guide, prepared by Glenn Austin with two collaborators and more than 100 contributing authors, represents a significant departure from the usual format of books on child care designed for parents. The major contribution is the emphasis on encouraging the parent to participate actively in the decision making process and to assume quite properly the responsibility for the day-to-day events and judgments that are required in child raising. In areas where there may be substantial differences of opinion between authorities, conflicting views and differences of opinion by various contributors are clearly outlined, and the parent is thus provided with the opportunity to choose among them for the approach which seems most comfortable at the time.

This volume is divided into nine major sections beginning with a discussion of the problems of parents and continuing through the characteristics of infancy; growth and development; basic training; school and learning problems; and separation, divorce and death.

Subjects covered that are particularly pertinent to our culture today include the interaction of the parents, the single parent family, adoption and alternate birth methods. Detailed instructions concerning breast feeding will be most helpful to many, while bottle feeding is discussed in a manner not likely to cause guilt and anxiety among those unable or unwilling to attempt breast feeding. The sections on understanding behavior and school and learning problems are particularly useful, and will assist parents in avoiding many of the problems frequently encountered.

It is difficult to identify serious omissions or inaccuracies, although I believe most readers would agree that the importance of immunization could have been emphasized in this book. Discussions of adolescence and the health and social problems of older children are not included. Similarly, accidents represent an important problem throughout childhood and have been neglected. The latter is not completely the case, since accidents and poisonings have been considered at length in the companion volume *The Parents' Medical Manual* prepared by the same authors. The importance of nutrition and sound advice in this area is also provided in the other volume.

The book is well written and should be understandable to average parents. The index is useful and the bibliography will be helpful to those interested in exploring particular topics in greater detail. This book can be recommended for parents to read in anticipation of the arrival of their infant, and will be a handy and useful reference to encourage the decision making process throughout infancy and as their child enters the school years.

PAUL F. WEHRLE, MD
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HOW TO HAVE INTERCOURSE WITHOUT GETTING SCREWED—Jennifer Wear, MSPH, and King Holmes, MD. Madrona Publishers, Inc., Seattle, Washington, 1976. 184 pages, $4.95 (Paperback).

This is a delightful book. It is informative, competently written, quite relevant, and scientifically and socially correct. The style is witty and engaging—those who have picked it up off my desk have not put it down until they have completely read it and all smiled when they returned it. It is *not* one of the recent spate of books on "doing it." Rather it seeks to inform about the potential consequences that follow that act and is written for "people who believe ignorance can be self-destructive, and want hard information that is not sugar-coated. It is for people who are sexually active or who think they might like to become sexually active someday—in or out of love, in or out of marriage, with or without children."

So what's "getting screwed"? It's the unwanted side effects of sex. Most of these arise from naive innocence and myth which this book dispels; it begins with male and female reproductive function and anatomy so readers can get a 3-D idea of their bodies and find out how their bodies work. On this foundation, all available methods of contraception are introduced including permanent contraception: vasectomy and tubal ligation. In the event of contraceptive failure or human error, a section on abortion is included. And, advice is given on what to do in regard to medical follow-up after rape.

The last part covers sexually transmitted diseases—from crabs to syphilis.

Jennifer Wear has taught classes in family planning, holds a master's degree in epidemiology from the University of Washington and is now a medical student at the University of California School of Medicine, San Francisco. King Holmes is a professor of medicine at the University of Washington who does research in the field of sexually transmitted diseases.

Look at the style and the attractive way information is presented: "Ever wonder why crabs concentrate in the pubic area? One theory is that crabs like to have intercourse, just like the rest of us. To do it, the male and female crabs have to grasp adjoining hairs two millimeters apart, and the spacing of the hairs is just about right in the pubic area. Crabs cannot jump and they cannot reach very far even when they stand on their tip-toes, so the only way to catch them is for your pubic hair to come within about two millimeters' distance from someone else's pubic hair or from where someone else's pubic hair has recently been. When the crab's tummys are full, they do occasionally drop off into your underpants, sheets, or sleeping bag, and curl up for a little nap . . . if you use a crab victim's clothing, bed, or sleeping bag within a day after he did, you could get screwed even without having intercourse." And then the book goes on to outline the treatment in just as attractive and realistic a style (gamma benzene [Kwell] or A-200 pyrinate).

We suggest having a copy in your office among those books you use for education of patients, especially for those of you who see young people. And those connected with schools might want to consider using it more broadly. Your own children will adore you for giving it to them.

H. HARRISON SADLER, MD
Clinical Professor of Psychiatry and Ambulatory Medicine
University of California, San Francisco
San Francisco

* * *

A SURVEY OF HUMAN DISEASES—David T. Purtilo, MD, Department of Pathology, School of Medicine, University of Massachusetts. Addison-Wesley Publishing Company, Medical/Nursing Division, 2725 Sand Hill Road, Menlo Park, CA (94025), 1978. 453 pages, $15.95.

How does one break down into neat, mutually exclusive categories the etiology, pathophysiology, pathology, diagnosis and treatment of the myriad diseases the human organism is heir to? Any breakdown must be arbitrary, and categories are bound to overlap. Consequently, criticism of any given breakdown is far simpler than coming up with a better alternative. In spite of the difficulty, however, there is a need for ". . . a textbook that surveys diseases and the pathophysiologic bases of diseases," which is the task Dr. Purtilo has set for himself. If he has not come up with the ideal solution to the impossible task of organizing a kaleidoscope in flux (I, for example, would have preferred juxtaposition of the two chapters that deal strictly with cells), he has, none the less, provided a logical, workable structure that allows complex subject matter to be presented in a clear, understandable way. Considering the vast area that falls under the title, *A Survey of Human Diseases*, the book strikes a remarkable balance between the too elementary and the too advanced. Aimed at an audience of nursing and allied health students, the presentation is straightforward and easy to follow without being condescending. In accomplishing this, the author presupposes some background in life science, while at the same time offering frequent explanations and definitions of concepts and words that may be unfamiliar to his readers. If he errs, it is on the side of clarity, but this is far better than straining for pretentious academic "rigorousness."

A strong feature of the book is its format. Each chapter opens with a chapter outline and list of objectives. Since readers will come to the book with varying levels of preparation, they will be able to select quickly and easily from outline and objectives, those sections of the book which meet their individual needs.

The text that follows the objectives is divided into sections whose headings correspond to the chapter outlines. Each text opens with a brief introduction of one or two paragraphs, and closes with a short summary. Finally, a separate bibliography related to the specific chapter subject matter concludes each chapter.

One minor negative note perhaps needs mention. Occasionally in the objectives those ubiquitous vague words "to know" and "to understand" pop up. Possibly this is an attempt to escape from monotonous repetition of the more precise and measurable "to list, describe, compare, discuss, explain, name or state," but the cost of such variety is fuzziness.

In spite of this, and a few other even more minor quibbles, one is forced to admit that Dr. Purtilo has bitten off more than anyone can chew, and then has pretty thoroughly chewed it. His selection from the limitless array of human diseases is reasonable (he does not pretend to cover *every* disease, but then neither does the *Merck Manual*), his organization of the material is workable, and the writing is easy to follow, especially since it is aided by many clear drawings, photographs and photomicrographs.

Where such a survey of diseases can be squeezed into health curricula the book will serve as an excellent text. In those programs in which requirements have so preempted available academic units that there remains no room for such a survey, the book will be useful as additional reading for students, since its format makes it, to a large extent, self-instructional. Finally, it can serve as a valuable reference book for advanced students, providing them with an overview and refresher of areas outside the narrowing fields of their specializations.

JEROME EPSTEIN, MA
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SYSTEMIC PATHOLOGY—Second Edition—Volume 3: ALIMENTARY SYSTEM—Edited by W. St C. Symmers, MD (Belfast), PhD (Birmingham), FRCP (London and Ireland), MRCP (Edinburgh), FRCPA, Professor of Histopathology in the University of London at Charing Cross Hospital Medical School; Honorary Consultant Pathologist, Charing Cross Hospital. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 465 pages, $45.00.

Volume 3 of *Systemic Pathology*, edited by W. St C. Symmers, is purported to be an "authoritative" modern, comprehensive and well-illustrated account of pathology of diseases in man. This particular volume describes the diseases of the gastrointestinal tract, including mouth, accessory organs, teeth, oropharynx, stomach, esophagus, small intestine, large intestine, anal canal, appendix, peritoneum, liver, gallbladder, and bile ducts in the pancreas. The individual chapters are authored by nine different pathologists, alone or in combination. In spite of the diversity of authorship there is a significant uniformity to the text, to the style and to the presentations. In each particular segment the coverage is extensive and encyclopedic. The illustrations, in general, are of good quality, and represent both gross photographs and light micrographs of representative diseases. Unusual and rare

diseases are included. There is a textual description, in some areas, of modern information concerning the nature of several diseases that are described.

Unfortunately, this continuity with the modern approach to pathology has not kept apace in the totality of the text. Reference to electron microscopy is made but electron micrographs do not appear. References to modern techniques are made but illustrative material does not accompany the text. In some areas the illustrations of specific features leave a lot to be desired. The malabsorption diseases in the bowel are only briefly covered and only two micrographs illustrate the changes that appear for the several types of malabsorption syndromes. Chronic gastritis is subdivided into a variety of different forms without providing the alternative view that these separations may be more artificial than real. Alcoholic liver disease is presented with, at best, poor illustration of alcoholic hyaline, and no further illustrative material is present to indicate its ultrastructural features. In this sense, the text represents a classical description of gross and microscopical pathology with a scattering of more contemporary knowledge. It is "essentially a pathologist's book on pathology" but this must be restricted to the individual with more an eye to practical relevance of day-to-day work rather than an understanding of the disease. The particularly heavy reference to parasitic disease and bacterial disease may reflect the difference in disease spectra seen in the British Isles in contrast to the experience of most North American pathologists. From this standpoint this exhaustive work provides a reference for existent and unusual disease, but does not provide more modern approaches as given in other more contemporary, also exhaustive, texts.

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BASIC SCIENCE OF NUCLEAR MEDICINE—Roy P. Parker, PhD, FInstP, Senior Lecturer in Medical Physics, Institute of Cancer Research, Royal Marsden Hospital, London; Peter H. S. Smith, BA, DPhil, Principal Physicist to the Clwyd and Gwynedd Health Authorities; Formerly Senior Physicist, Royal Marsden Hospital, London; David M. Taylor, PhD, DSc FRIC, Senior Lecturer and Head of the Radiopharmacology Department, Institute of Cancer Research, Royal Marsden Hospital, London. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 374 pages, $19.50.

This text is a comprehensive survey of the field of nuclear medicine. Except for emission computerized tomography the book covers every aspect of nuclear medicine with sufficient detail to provide all nuclear medicine personnel with a working knowledge of this medical specialty.

The book is organized in five parts: (1) basic physics, (2) radiation and biology, (3) measurement and instrumentation, (4) basic chemistry and (5) radiopharmaceuticals. Each part starts with the basic principles necessary for understanding the material in that section. The mathematics, physics or chemistry is developed in a clear and concise manner and should be understandable to those who may be unfamiliar with these subjects or have found them difficult to comprehend before. Following the development of a concept a simple problem is worked out to show how that concept is applied in actual practice. Liberal use of simple, easy-to-read charts and graphs helps to organize and clarify the material for the reader. Although the authors have concentrated on the basic sciences many practical hints for actually working in a nuclear medicine department are included.

Section I (basic physics) reviews the usual topics of radiation and matter with their structure, production, interaction and decay. In this section as in all other sections chapters are short and concise.

Radiation and biology, section II, discusses dosimetry, biological effects of radiation, principles of choosing a radiopharmaceutical, and tracer techniques. Dosimetry makes use of the MIRD reports.

Section III, measurement and instrumentation, begins with a short introduction of measurement errors and then discusses various types of radiation detection equipment. The use of collimators with the various detectors is succinctly summarized. At the end of the section a chaper is devoted to the selection of operating parameters for the best nuclear medicine scan.

Basic chemistry, section IV, reviews chemical bonds, pH and buffer solutions, hydrolysis and complex formation, colloids, proteins, and the chemistry of some of the elements important to nuclear medicine.

The fifth section, radiopharmaceuticals, discusses the different production methods of radionuclides and their relative merits. Generator systems are introduced and the ^{99}Mo-^{99m}Tc generator is covered in detail with other systems being listed. General production and testing of radiopharmaceuticals is described. Kits for preparing bone-imaging and liver-imaging agents illustrate the use of radiopharmaceuticals in the nuclear medicine department. A review of laboratory facilities and safety procedures is included.

Subjects are not footnoted in the text, but there is cross referencing between chapters on certain subjects. SI units are used with the more familiar units retained. Appendices are included which have basic mathematics and derivations, SI units, symbols used in nuclear medicine, useful physical data for dosimetry and sample problems with answers. Although a bibliography is not included with each chapter, the bibliography at the end of the text lists books that discuss in greater detail subjects dealt with in this text. The book also includes an index.

This book should be useful to all who work in nuclear medicine as a basic science text and as general instruction for those working in related areas. It should also be valuable to those doing a comprehensive review for examinations.

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Co-Director, Thyroid Oncology Service
City of Hope National Medical Center
Duarte, California
Clinical Assistant Professor of Radiological Sciences, UCLA Medical Center, Los Angeles

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ANNUAL REVIEW OF NEUROSCIENCE—Volume 1, 1978—Editor: W. Maxwell Cowan, Washington University School of Medicine, St. Louis; Associate Editors: Zach W. Hall, University of California School of Medicine; and Eric R. Kandel, College of Physicians and Surgeons of Columbia University, New York. Annual Reviews, Inc., 4139 El Camino Way, Palo Alto, CA (94306), 1978. 506 pages, $17.00.

The field of neuroscience, the interdisciplinary approach to the study of the nervous system, has made great strides during the past decade. This is due largely to the development of new and sophisticated techniques in the field of molecular and cell biology that are readily applicable to the study of the nervous system. Advances include the analysis of gene expression in neurons, the study of the long-term consequences of synaptic activity, and the elucidation of the molecular structure of neuronal membranes and their associated ion channels and receptors. New techniques in the field of neuronanatomy

have permitted the identification of transmitter-specific neuronal populations and the tracing of neuronal connections.

The *Annual Review of Neuroscience* was stimulated by the ever-increasing productivity of this discipline and the interest it has provoked among biologically oriented scientists. It intends to cover both the vertebrate and invertebrate nervous systems. The review, according to the editors, will deal with certain aspects of the related clinical disciplines of neurology, neurosurgery, and psychiatry, as well as with the so-called basic neurosciences. The series will afford broad coverage and thus will include both highly technical and theoretical chapters. Some volumes will have definite clinical applications, while others will have a more basic orientation.

Volume I contains chapters on the following subjects: environmental determination of autonomic neurotransmitter functions; circadian pacemakers in the nervous system; neural control of behavior; motor systems, with specific reference to the control of locomotion; pain; sensory evoked potentials in clinical disorders of the nervous system; central catecholamine neuron systems: anatomy and physiology of the dopamine systems; optical methods for monitoring neuron activity; regulation of autonomic development; recent advances in neuroanatomical methodology; mechanisms of cortical development: a view from mutations in mice; trophic mechanisms in the peripheral nervous system; auditory mechanisms of the lower brainstem; neurophysiology of epilepsy; biology of cultured nerve and muscle, and organization of neuronal membranes. The authors selected for the various chapters are recognized authorities in their respective fields of interest. The chapters are generally well written and adequately illustrated. Some require a fundamental knowledge of basic neuroscience, being highly technical, while others are more readily accessible to clinicians or researchers in some other biological discipline. While not exhaustive, the references include the up-to-date and relevant literature on a given topic.

Whereas the book is aimed primarily at basic neuroscientists and academically oriented clinical neurologists, there are a number of chapters that should be useful to practicing neurologists—for example, those chapters dealing with evoked potentials and epilepsy. The broad scope covered by this reasonably brief first volume is particularly useful to those academicians who are responsible for the teaching of neuroscience and neurology and who need up-to-date information on topics outside of their own expertise.

Professor W. Maxwell Cowan of Washington University School of Medicine in St. Louis and the review's editorial committee have already selected the subjects for the second volume, which will be published later in 1979. A number of exciting topics will be included—opiate receptors and endorphins, the biology of affective disorders, memory, slow viral infections, to name a few.

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RETROSPECTROSCOPE—Insights Into Medical Discovery—Julius H. Comroe, Jr., MD, Morris Herzstein Professor of Biology, Cardiovascular Research Institute, and Professor of Physics, University of California, San Francisco. The Von Gehr Press, P.O. Box 7654, Menlo Park, CA (94025), 1977. 182 pages, $5.00 (Paperback).

The Retrospectroscope illuminates in useful and engaging ways the events which led to a number of important scientific and biomedical discoveries. It illustrates the elements of foresight and chance, open-mindedness and dogmatism, fact and fancy that enter into the scientific process. It underscores the unforeseen benefits of scientific curiosity: the results of exploring why the sky is blue are particularly striking. The book is written in a refreshing way and provides fine documentation. Bits and pieces may be usefully read separately from the remainder of the text. One is simultaneously enlightened and entertained.

If the book were merely an account of the discoveries and the human interactions surrounding them, with lessons on intellectual behavior, no substantive criticism would be in order. However, *The Retrospectroscope* essays are part of a policy study. As the preface recounts, the study grew out of policy debates concerning financial support of basic science. The results have been interpreted by many as documentary evidence that scientists, including biomedical investigators, should be allowed to ply their trade with ample public funding but free of public scrutiny or participation because that is the only path to true knowledge.

Such an interpretation is unwarranted. Unfortunately, as a policy document *The Retrospectroscope* is limited. This is so for many reasons. First, it perceives of science in its earlier form as an individual enterprise of a few clever people working largely alone against a mountain of ignorance. Modern, team-based "big" science is barely mentioned, much less analyzed. Second, the history which is examined is that of personal actions in individual cases; science is not recognized as a social enterprise with a system of values, rewards and punishments, or as a changing body of knowledge affected by varying perceptions of natural and social reality, or as an economic entity. Third, that there are different strategies and tactics of scientific investigation, with successes and failures of the different methodologies and continuous conflicts about them is nowhere to be found. Fourth, the capacity of modern science and technology to alter nature and society drastically is not discussed, much less recognized as a substantial policy issue. Yet this capacity underlies much of contemporary concern with science. These deficiencies of *The Retrospectroscope*'s vision vitiate its usefulness as a policy document. At best, it provides only a partial view of those factors which promote creative insight or improve health.

Certainly basic science is a cornerstone of modern medicine. However, biomedical practitioners have generally belittled and excluded from their institutions other types of scholarship outside natural science, such as epidemiology, sociology, economics and related disciplines. As a consequence, nonbiological influences on health, or on biological processes themselves, are rarely examined. This consequence is quite damaging to understanding of health and disease, and to training of health professionals. The relative ineffectiveness and inefficiency of contemporary medical practice witness this inadequacy.

The idea that natural scientists left to their own devices will provide answers to health or other problems will not wash in 1978, even taking into account the insights derived by Comroe. To imply that possibility, exposes the problem with much of scientific leadership today: it is inadequately informed for the task before it.

Julius Comroe is a giant of modern biomedicine, a a superb teacher and a delightful person. The book is charming and informative. But a policy document it is not. Read it for what it is and you will be well rewarded; read it for what it is not, and you will be misled.

HALSTED R. HOLMAN, MD
Professor of Medicine
Stanford University School of Medicine
Stanford, California

in memoriam

Abbott, Steven L., Upland. Died July 24, 1978, aged 35. Graduate of University of California Irvine College of Medicine, 1973. Licensed in California in 1974. Dr. Abbott was a member of the San Bernardino County Medical Society.

Albi, R. William, Spokane. Died March 12, 1979 in Spokane, aged 76. Graduate of Loyola University Stritch School of Medicine, Chicago, 1933. Licensed in Washington state in 1949. Dr. Albi was a member of the Spokane County Medical Society.

Anderson, Charles M., Spokane. Died February 12, 1979 in Spokane, aged 88. Graduate of the University of Michigan Medical School, Ann Arbor, 1917. Licensed in Washington state in 1926. Dr. Anderson was a member of the Spokane County Medical Society.

Anderson, Harold T., Spokane. Died December 2, 1978 in Spokane, aged 77. Graduate of the University of Minnesota Medical School, Minneapolis, 1926. Licensed in Washington state in 1947. Dr. Anderson was a member of the Spokane County Medical Society.

Ervin, Clinton V., jr., San Mateo. Died June 3, 1979 in San Mateo of heart disease, aged 67. Graduate of Vanderbilt University School of Medicine, Nashville, 1934. Licensed in California in 1935. Dr. Ervin was a member of the San Mateo County Medical Society.

Fowler, Charles Beebe, Aptos. Died June 15, 1979 in Mill Valley, aged 86. Graduate of the University of California Medical School, Berkeley-San Francisco, 1920. Licensed in California in 1920. Dr. Fowler was a retired member of the Santa Cruz County Medical Society.

Garman, James E., Spokane. Died December 28, 1978 in Spokane, aged 47. Graduate of the University of Iowa College of Medicine, Iowa City, 1955. Licensed in Washington state in 1968. Dr. Garman was a member of the Spokane County Medical Society.

Geistweit, William Henry, jr., San Diego. Died June 13, 1979 in North Park, aged 86. Graduate of Washington University School of Medicine, St. Louis, 1919. Licensed in California in 1920. Dr. Geistweit was a retired member of the San Diego County Medical Society.

Graybill, Martin B., Escondido. Died July 6, 1979 in Escondido of heart disease, aged 82. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1924. Licensed in California in 1924. Dr. Graybill was a member of the San Diego County Medical Society.

Gross, Alvin J., San Francisco. Died July 10, 1979, aged 65. Graduate of Creighton University School of Medicine, Omaha, 1941. Licensed in California in 1954. Dr. Gross was a member of the San Francisco Medical Society.

Harley, Garth Howland, Monterey. Died March 25, 1979 in Pebble Beach, aged 68. Graduate of the University of Buffalo School of Medicine, Buffalo, NY, 1939. Licensed in California in 1969. Dr. Harley was a member of the Monterey County Medical Society.

Hill, George, Torrance. Died July 11, 1979 in Torrance of gunshot wounds, aged 35. Graduate of Columbia University College of Physicians and Surgeons, New York, 1971. Licensed in California in 1972. Dr. Hill was a member of the Los Angeles County Medical Association.

Hunter, Harry D., Wenatchee. Died March 19, 1979 in Wenatchee of myocardial infarction, aged 62. Graduate of the University of Rochester School of Medicine and Dentistry, Rochester, 1945. Licensed in Washington state in 1953. Dr. Hunter was a member of the Chelan-Douglas County Medical Society.

Jacobson, George, Los Angeles. Died March 18, 1979, aged 66. Graduate of the University of California Medical School, Berkeley-San Francisco, 1938. Licensed in California in 1938. Dr. Jacobson was a retired member of the Los Angeles County Medical Association.

Johnson, George E., Whittier. Died December 14, 1978, aged 91. Graduate of Loyola University Stritch School of Medicine, 1918. Licensed in California in 1947. Dr. Johnson was a retired member of the Los Angeles County Medical Association.

Kepl, Maxwell F., Spokane. Died March 10, 1979 in Spokane, aged 64. Graduate of Northwestern University Medical School, Chicago, 1940. Licensed in Washington state in 1946. Dr. Kepl was a member of the Spokane County Medical Society.

Klinefelter, Robert P., Salinas. Died June 17, 1979 of injuries received in gyrocopter mishap near Paso Robles, aged 67. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1943. Licensed in California in 1943. Dr. Klinefelter was a member of the Monterey County Medical Society.

Klussmann, Hans, San Francisco. Died June 28, 1979 in San Francisco, aged 90. Graduate of Rheinische Friedrich-Wilhelms-Universität Medizinische Fakultät, Bonn, Prussia, 1914. Licensed in California in 1915. Dr. Klussmann was a retired member of the San Francisco Medical Society.

LACEY, LLOYD E., Los Angeles. Died in May 1979, aged 84. Graduate of the State University of Iowa College of Medicine, Iowa City, 1920. Licensed in California in 1923. Dr. Lacey was a retired member of the Alameda-Contra Costa Medical Association.

LARSEN, JAMES D., Spokane. Died February 20, 1979 in Spokane, aged 48. Graduate of the University of Iowa College of Medicine, Iowa City, 1963. Licensed in Washington state in 1964. Dr. Larsen was a member of the Spokane County Medical Society.

LEICESTER, KATHERINE HAWORTH, Greenbrae. Died June 10, 1979 in Greenbrae, aged 80. Graduate of the University of California Medical School, Berkeley-San Francisco, 1920. Licensed in California in 1920. Dr. Leicester was a retired member of the Marin Medical Society.

LUNDQUIST, DELL T., Palo Alto. Died March 17, 1979, aged 79. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1927. Licensed in California in 1927. Dr. Lundquist was a retired member of the Santa Clara County Medical Society.

PARRETT, VIRGIL O., Napa. Died June 3, 1979 in a plane crash near Encinitas, aged 66. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1937. Licensed in California in 1937. Dr. Parrett was a member of the Napa County Medical Society.

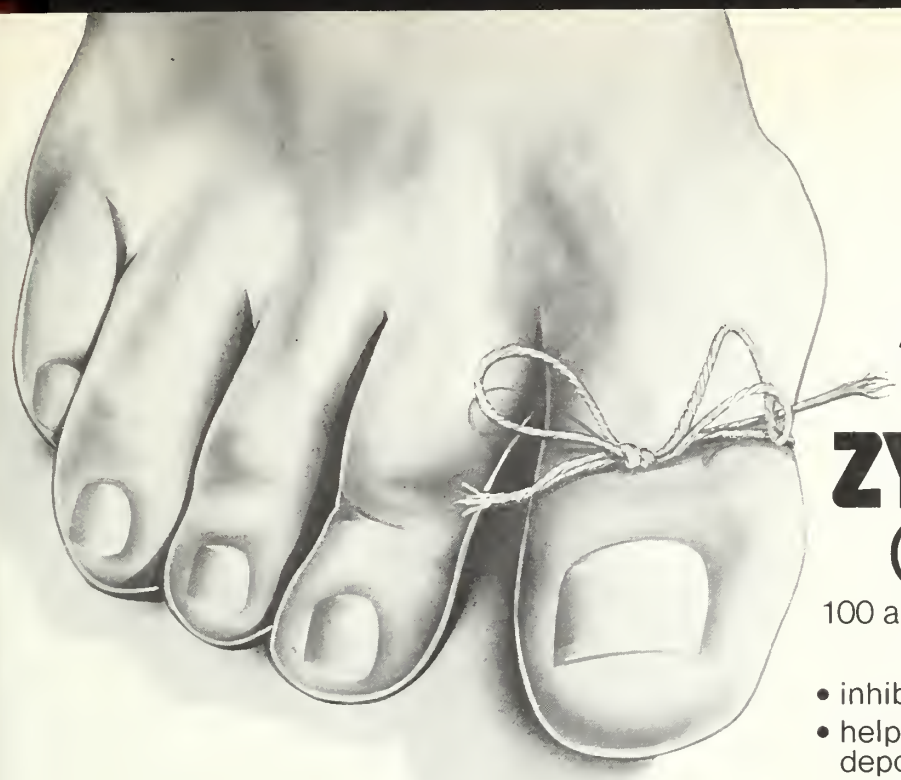
PLANTING, PURL L., Calimesa. Died May 17, 1979 in Calimesa, aged 73. Graduate of the University of Chicago, The School of Medicine, 1936. Licensed in California in 1941. Dr. Planting was a retired member of the Los Angeles County Medical Association.

PRITCHARD, WALTER, Costa Mesa. Died August 28, 1978, aged 84. Graduate of Stanford University School of Medicine, San Francisco-Palo Alto, 1921. Licensed in California in 1921. Dr. Pritchard was a retired member of the San Bernardino County Medical Society.

WARNOCK, ARCHIBALD W., San Pedro. Died June 7, 1979, aged 83. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1923. Licensed in California in 1923. Dr. Warnock was a member of the Los Angeles County Medical Association.

WHITMER, DANIEL WARREN, Carmichael. Died June 21, 1979 in Carmichael, aged 42. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1961. Licensed in California in 1965. Dr. Whitmer was a member of the Sacramento County Medical Society.

WOOLSEY, JOHN HOMER, Woodland. Died June 21, 1979 in Woodland, aged 90. Graduate of the University of California Medical School, Berkeley-San Francisco, 1915. Licensed in California in 1915. Dr. Woolsey was a retired member of the Yolo County Medical Society.



A reminder

ZYLOPRIM®

(allopurinol)

100 and 300 mg scored Tablets

- inhibits uric acid formation
- helps prevent urate crystal depositions in synovia
- reduces risk of uric acid lithiasis

NDICATIONS AND USE: This is not an innocuous lrug and strict attention should be given to the ndications for its use. Pending further investiga- ion, its use in other hyperuricemic states is not ndicated at this time.

'yloprim® (allopurinol) is intended for:

treatment of gout, either primary, or secondary to the hyperuricemia associated with blood dyscrasias and their therapy;

treatment of primary or secondary uric acid nephropathy, with or without accompanying symptoms of gout;

treatment of patients with recurrent uric acid stone formation;

prophylactic treatment to prevent tissue urate deposition, renal calculi, or uric acid nephropathy in patients with leukemias, lymphomas and malignancies who are receiving cancer chemotherapy with its resultant elevating effect on serum uric acid levels.

ONTRAINDICATIONS: Use in children with the xception of those with hyperuricemia secondary to alignancy. The drug should not be employed in nursing others.

atients who have developed a severe reaction to yloprim should not be restarted on the drug.

/ARNINGS: ZYLOPRIM SHOULD BE DISCONTINUED T THE FIRST APPEARANCE OF SKIN RASH OR ANY GN OF ADVERSE REACTION. In some instances a skin sh may be followed by more severe hypersensitivity actions such as exfoliative, urticarial and purpuric sions as well as Stevens-Johnson syndrome (erythema ultiforme) and very rarely a generalized vasculitis which ay lead to irreversible hepatotoxicity and death.

few cases of reversible clinical hepatotoxicity have en noted and in some patients asymptomatic rises in rum alkaline phosphatase or serum transaminase have en observed. Accordingly, periodic liver function tests ould be performed during the early stages of therapy rticularly in patients with pre-existing liver disease.

tients should be alerted to the need for due precaus ns when engaging in activities where alertness is andatory.

vertheless, iron salts should not be given simultaously with Zyloprim. This drug should not be ministered to immediate relatives of patients with opathic hemochromatosis.

patients receiving Purinethol® (mercaptorine) or Imuran® (azathioprine), the concomitant ministration of 300-600 mg of Zyloprim per day l require a reduction in dose to approximately e-third to one-fourth of the usual dose of mercapurine or azathioprine. Subsequent adjustment doses of Purinethol or Imuran should be made the basis of therapeutic response and any ic effects.

Usage in Pregnancy and Women of Childbearing Age. Zyloprim® (allopurinol) should be used in pregnant women or women of childbearing age only if the potential benefits to the patient are weighed against the possible risk to the fetus.

PRECAUTIONS: Some investigators have reported an increase in acute attacks of gout during the early stages of allopurinol administration, even when normal or subnormal serum uric acid levels have been attained.

It has been reported that allopurinol prolongs the half-life of the anticoagulant, dicumarol. This interaction should be kept in mind when allopurinol is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

A fluid intake sufficient to yield a daily urinary output of at least 2 liters and the maintenance of a neutral or, preferably, slightly alkaline urine are desirable to (1) avoid the theoretic possibility of formation of xanthine calculi under the influence of Zyloprim therapy and (2) help prevent renal precipitation of urates in patients receiving concomitant uricosuric agents.

Patients with impaired renal function require less drug and should be carefully observed during the early stages of Zyloprim administration and the drug withdrawn if increased abnormalities in renal function appear.

In patients with severely impaired renal function, or decreased urate clearance, the half-life of oxipurinol in the plasma is greatly prolonged. Therefore, a dose of 100 mg per day or 300 mg twice a week, or perhaps less, may be sufficient to maintain adequate xanthine oxidase inhibition to reduce serum urate levels. Such patients should be treated with the lowest effective dose, in order to minimize side effects.

Mild reticulocytosis has appeared in some patients.

As with all new agents, periodic determination of liver and kidney function and complete blood counts should be performed especially during the first few months of therapy.

ADVERSE REACTIONS:

Dermatologic: Because in some instances skin rash has been followed by severe hypersensitivity reactions, it is recommended that therapy be discontinued at the first sign of rash or other adverse reaction (see WARNINGS). Skin rash, usually maculopapular, is the adverse reaction most commonly reported.

Exfoliative, urticarial and purpuric lesions, Stevens-Johnson syndrome (erythema multiforme) and toxic epidermal necrolysis have also been reported.

A few cases of alopecia with and without accompanying dermatitis have been reported.

In some patients with a rash, restarting Zyloprim (allopurinol) therapy at lower doses has been accomplished without untoward incident.

Gastrointestinal. Nausea, vomiting, diarrhea, and intermittent abdominal pain have been reported.

Vascular. There have been rare instances of a generalized hypersensitivity vasculitis or necrotizing angiitis which have led to irreversible hepatotoxicity and death.

Hematopoietic: Agranulocytosis, anemia, aplastic anemia, bone marrow depression, leukopenia, pancytopenia and thrombocytopenia have been reported in patients, most of whom received concomitant drugs with potential for causing these reactions. Zyloprim® (allopurinol) has been neither implicated nor excluded as a cause of these reactions.

Neurologic: There have been a few reports of peripheral neuritis occurring while patients were taking Zyloprim. Drowsiness has also been reported in a few patients.

Ophthalmic. There have been a few reports of cataracts found in patients receiving Zyloprim. It is not known if the cataracts predated the Zyloprim therapy. "Toxic" cataracts were reported in one patient who also received an anti-inflammatory agent; again, the time of onset is unknown. In a group of patients followed by Gutman and Yü for up to five years on Zyloprim therapy, no evidence of ophthalmologic effect attributable to Zyloprim was reported.

Drug Idiosyncrasy. Symptoms suggestive of drug idiosyncrasy have been reported in a few patients. This was characterized by fever, chills, leukopenia or leukocytosis, eosinophilia, arthralgias, skin rash, pruritus, nausea and vomiting.

OVERDOSAGE: Massive overdosing, or acute poisoning, by Zyloprim has not been reported.

HOW SUPPLIED: 100 mg (white) scored tablets, bottles of 100 and 1000; 300 mg (peach) scored tablets, bottles of 30, 100 and 500. Unit dose packs for each strength also available.

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See following page for brief summary

PRONESTYL® TABLETS
Procainamide Hydrochloride Tablets

The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate considerations of alternative anti-arrhythmic therapy.

DESCRIPTION: Pronestyl (Procainamide Hydrochloride) is the amide analogue of procaine hydrochloride and is available for oral administration as veneer-coated tablets providing 250 mg, 375 mg, and 500 mg procainamide hydrochloride.

CONTRAINDICATIONS: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; bear in mind cross sensitivity to procaine and related drugs. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of second degree and third degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: Evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgment of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with oral maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

ADVERSE REACTIONS: Hypotension is rare with oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported in patients on oral maintenance therapy (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

For full prescribing information, consult package insert.

HOW SUPPLIED: Pronestyl Tablets (Procainamide Hydrochloride Tablets) providing 250 mg, 375 mg, and 500 mg procainamide hydrochloride are available in bottles of 100 and Unimatic® single-dose packaging in cartons of 100. The 250 mg and 500 mg tablets are also available in bottles of 1000.

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The Maker

Examining a Few Myths About Prescribing.

Increasing pressure is being put on the practicing physician to prescribe drugs generically. You are told that brand–name products are universally "expensive" and generic versions are relatively "cheap." To make this case, the most extreme (rather than typical) price differentials are cited. Thus, consumers are led to believe that such differentials are commonplace. Even your knowledge and your motives as a physician are questioned.

Understandably, these views have created myths. We think it's time to examine them in the light of all the facts and ramifications.

MYTH: There are no differences in quality and performance between brand-name products and their generic counterparts. The corollary is that there are no differences among products made by high-technology, quality-conscious, research-based companies and those made by commodity-type suppliers.

FACT: The Food and Drug Administration does a good job in monitoring a generally excellent drug supply. Still, it has nowhere near the resources to guarantee the quality and bioavailability of all marketed products at any given time. Just a few months ago, for example, it noted that batches of tetracycline HCl capsules which met official monograph requirements were not bioequivalent to a reference product. As you know, there is substantial literature on this subject affecting many drugs, including such antibiotics as tetracycline and erythromycin. The record on drug recalls and court actions affirms strongly that there are differences among pharmaceutical companies and their products. Research-intensive companies have far better records than those that do no research and may practice minimum quality assurance.

MYTH: Industry favors only "expensive" brand names and denigrates all generics.

FACT: PMA companies make 90 to 95 percent of the drug supply, including, therefore, most of the generics. Drug nomenclature is not the important point; it's the competence of the manufacturer and the integrity of the product that count.

Matters.

MYTH: Generic options almost always exist.

FACT: About 55 percent of prescription drug expenditure is for single-source drugs. This means, of course, that for only 45 percent of such expenditure, is a generic prescribing option available.

MYTH: Generic prescriptions are filled with inexpensive generics, thus saving consumers large sums of money.

FACT: Market data show that you invariably prescribe—and pharmacists dispense—both brand and generically labeled products from known and trusted sources, in the best interest of patients. In most cases the patient receives a proven brand product. Savings from voluntary or mandated generic prescribing are grossly exaggerated.

MYTH: Drugs account for a major portion of the rise in health care costs.

FACT: Drugs represent a very small part of such costs. The amount of the health care dollar spent for prescription drugs was about 12 cents in 1967; today it is about 8 cents. And you as a physician are most conscious of how drug therapy can cut hospitalization, avert surgery, reduce office visits and keep patients on the job.

MYTH: Government intrusions into the marketplace will save tax money.

FACT: Government schemes always cost the taxpayer something, and the costs often exceed the benefits. Certainly, any federal "help," such as lists of wholesale drug prices sent to all physicians and pharmacists, will be no exception. Just think of the expense of keeping them current! Moreover, wholesale prices are poor guides to actual transaction prices and even worse guides to retail prices.

The PMA Position

We believe your freedom to prescribe, either by generic or brand name, should be totally unabridged. Otherwise, your prescribing prerogatives and your relationships with patients will be seriously impaired.

The maker does matter

After the myths about price and equivalency have been shattered, one fact stands out more clearly than ever: *The maker does matter.* As always, your best guide to drug therapy for your patients is to select products—both brands and generics—from manufacturers with credentials and performance records you have come to respect.

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(Continued on Page 28)

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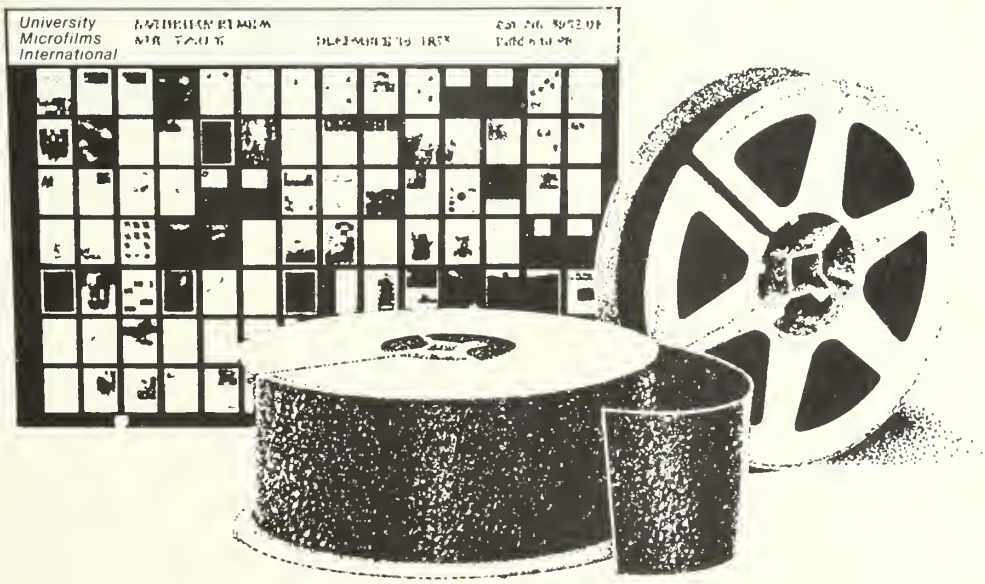

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(Continued from Page 26)

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(Continued on Page 30)

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(Continued from Page 28)

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ANESTHESIOLOGY

August 18—**Current Concepts in Anesthesia.** Kaiser-Permanente at Red Lion Inn, Sacramento. Saturday. 6 hrs. Contact: B. L. Vandermeer, MD, Chief of Anesthesia, Kaiser Foundation Hosp., 2025 Morse Ave., Sacramento 95825. (916) 486-5011.

September 15-22—**Practical Management of Anesthetic Problems.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 31½ hrs. $325.

October 20-24—**American Society of Anesthesiologists—Annual Meeting.** San Francisco. Saturday-Wednesday. Contact: William S. Marinko, Asst. Exec. Sec., ASA, 515 Busse Highway, Park Ridge, IL 60068. (312) 825-5586.

October 25-November 2—**Post ASA Hawaiian Seminar.** Kona Village Resort, Hawaii. 9 days. 28 hrs. Contact: Adham Safwat, Box 7550, Menlo Park 94025. (415) 494-3799.

October 26-28—**Clinical Anesthesia Monitoring.** Anesthesiology Educational Foundation and Calif. Soc. of Anesthesiologists at Holiday Inn, Monterey. Friday-Sunday. Contact: AEF, P.O. Box 24230, Federal Bldg., Los Angeles 90024.

CANCER

September 15—**Histopathology of Head and Neck Tumors.** Head and Neck Cancer Network of the No. Calif. Cancer Program and San Francisco Regional Cancer Foundation at Children's Hospital, San Francisco. Saturday. 8 hrs. Contact: SF Regional Cancer Fnd., 14th and Lake, San Francisco 94118. (415) 221-2132.

September 15-16—**Advances in the Cause, Detection and Prevention of Cancer: A Multi-Disciplinary Analysis.** UCSF at Sheraton-Palace, San Francisco. Saturday-Sunday.

September 20-22—**Bladder Cancer.** American Urological Assn. at Hilton Hotel, San Diego. Thursday-Saturday. 16 hrs. $200, members; $250, nonmembers. Contact: Mary Rohan, AUA Office of Education, P.O. Box 1129, Aspen, CO 81611. (303) 925-2012.

September 26—**Head and Neck Cancer Symposium.** Hospital of the Good Samaritan, Los Angeles. Wednesday. 7 hrs. Contact: Janie Sternal, CME Coordinator, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

October 12—**John W. Cline Memorial Lecture.** American Cancer Society, Calif. Division, at Woodlake Inn, Sacramento. Friday. Contact: Education Dept., ACS, 731 Market, San Francisco 94103. (415) 777-1800.

October 13-20—**New Approaches to the Evaluation of Neoplastic Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 33½ hrs. $375.

October 27—**New Methods for Fighting Cancer.** San Francisco Regional Cancer Foundation at Letterman Army Hospital, San Francisco. Saturday. 4 hrs. Contact: Dr. Terry Sheehy, S.F. Regional Cancer Foundation, 14th and Lake, San Francisco 94118. (415) 221-2132.

October 31-November 2—**Cancer Symposium—3rd Annual.** Scripps Memorial Hospital at Holiday Inn at the Embarcadero, San Diego. Wednesday-Friday. 22 hrs. $250. Contact: Nomi Feldman, Conf. Coordinator, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

November 9-10—**Gynecologic and Breast Cancer: Current Concepts and Controversies.** Mt. Zion Hospital and Medical Center at Fairmont Hotel, San Francisco. Friday-Saturday. Contact: Office of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

December 12—**15th Annual Northern California Cancer Conference.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 7 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Memorial Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 284.

EMERGENCY MEDICINE

September 8—**Orange County Emergency Workshop Part III—Neurological Trauma.** UCI. Saturday. 5 hrs.

September 12—**Emergency Radiology.** See Radiology and Pathology, September 15.

September 17-21—**Topics in Emergency Medicine.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Monday-Friday. 40 hrs. $325.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

September 24—**Trauma—Auto and Motorcycle Patients.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

September 24-28—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Monday-Friday. 40 hrs. $350.

October 8-12—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

December 6-8—**Trauma.** See Surgery, December 6-8.

December 10-14—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $350.

MEDICINE

August 16-18—**Podiatric Dermatology Symposium.** STAN. Thursday-Saturday. 17 hrs. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

August 27-31—**Update in Internal Medicine.** Mills Memorial Hospital at Golden Gateway Holiday Inn, San Francisco. Monday-Friday. 32 hrs. $200. Contact: Robert Siegel, MD, Med. Staff Office, Mills Memorial Hosp., 100 S. San Mateo Dr., 94401. (415) 342-5667.

August 29-31—**Skin Microbiology: Relevance to Clinical Infection.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday. 18 hrs. $190.

September 6-9—**Review of Internal Medicine.** UCSD at Sheraton Inn Airport, San Diego. Thursday-Sunday. 28 hrs. $275.

September 9-14—**Non-Invasive Diagnostic Technique in Vascular Disease.** UCSD at Sheraton Harbor Island Hotel, San Diego. Sunday-Friday. 35 hrs. $300.

September 10-13—**Electrocardiography: Core Curriculum and Self-Assessment.** American College of Cardiology at Fairmont Hotel, San Francisco. Monday-Thursday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

September 12—**Epilepsy—Its Diagnosis and Treatment.** LLU. Wednesday. 4 hrs.

September 16-20—**Pacific Dermatologic Association—Annual Meeting.** Hyatt Regency, San Francisco. Sunday-Thursday. 15½ hrs. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno NV 89509. (702) 323-2461.

September 24-28—**An Advanced Course for Internists.** STAN at San Francisco. Monday-Friday.

September 28-30—**Coronary Disease, Exercise Testing and Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton on the Wharf, San Francisco. Friday-Sunday. 13 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

October 3-4—**47th Annual Fall Symposium and 12th George C. Griffith Scientific Lecture.** American Heart Assn., Greater Los Angeles Affiliate, at Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hrs. $85, member any Heart Assn.; $110, nonmember. Contact: Alexis Krieger, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

October 5-6—**Controversial Issues in Internal Medicine—24th Annual Symposium.** Southern California Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, Ed. and Research Dept., SCPMG, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

October 6—**Office Allergy.** PMC. Saturday. 6 hrs. $85.

October 8—**Calcium Metabolism.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

October 10—**Rheumatoid Arthritis—Its Diagnosis and Treatment.** LLU. Wednesday. 4 hrs.

October 11-12—**49th Annual Physicians' Postgraduate Symposium on Cardiovascular Disease.** American Heart Assn., San Francisco Chapter, at San Franciscan Hotel, San Francisco. Thursday-Friday. Contact: Patty MacJennett, AHA, 421 Powell St., San Francisco 94108. (415) 433-2273, ext. 443.

October 13—**Lupus Erythematosus.** UCSD. Saturday. 6 hrs. $45.

October 15-19—**Advanced Course for Internists.** STAN at Hyatt on Union Square, San Francisco. Monday-Friday. 25 hrs. $290.

October 18-20—**Cardiology Update—1979.** American College of Cardiology at Del Monte Hyatt, Monterey. Saturday-Monday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

October 18-20—**Rheumatology Update—1979.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Saturday. 16 hrs. $165.

October 18-21—**Society of Nuclear Medicine—4th Annual Western Regional Meeting.** Monterey Conference Center, Monterey. Thursday-Sunday. Contact: Justine Parker, Western Regional Chapters, Society of Nuclear Medicine, P.O. Box 40279, San Francisco 94140. (415) 647-0722.

October 19-20—**Mycology Review** (a course for residents in dermatology and pathology). STAN. Friday-Saturday. 16 hrs. $50 per day; $25 per day for residents and trainees. Contact: Paul H. Jacobs, MD, Dept. of Derm., Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

October 19-20—**Vascular Disorders and the Primary Care Physician.** UCSF at Fairmont Hotel, San Francisco. Friday-Saturday. 11 hrs. $130, both days; $80, one day.

October 20-27—**British Clinical Cardiology in the Paul Wood Tradition.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $325.

October 22—**Respiratory Diseases Due to Pollutants.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

November 2-3—**California Society of Internal Medicine—Annual Meeting.** Hotel del Coronado, Coronado. Friday-Saturday. Contact: CSIM, 703 Market St., 1412 Central Tower, San Francisco 94103. (415) 362-1548.

November 3—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Sch. of Med., Stanford 94305. (415) 497-6101.

November 4-6—**Fifth Annual Workshop on the Thyroid.** American Thyroid Assn. at Golden Gateway Holiday Inn, San Francisco. Sunday-Tuesday. 14 hrs. $200. Contact: Dr. Lewis Braverman, Univ. of Mass. Med. Ctr., 55 Lake Ave., N., Worchester, MA 01605.

November 5-9—**Update on Dermatology and Rheumatology for the Practicing Physician.** Scripps Clinic and Research Foundation at Islandia Hyatt, San Diego. Monday-Friday. 35 hrs. $325. Contact: Nomi Feldman, Conf. Coordinator, Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100, ext. 8214.

November 5-14—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

November 8-10—**Coronary Artery Disease: Medical and Surgical Decisions.** Eisenhower Medical Center at Marriott Las Palmas Resort, Rancho Mirage. Thursday-Saturday. Contact: John J. Deller, MD, Dir. of Ed. and Research, Eisenhower Med. Ctr., 39000 Bob Hope Dr., Palm Desert 92260. (714) 346-3911.

November 9—**Venous Thromboembolism.** PMC and American Heart Assn. Friday. 6 hrs. $25.

November 10—**Viral Diseases in Clinical Practices.** Alta Bates Hospital, Berkeley. Saturday. 6 hrs. Contact: Claudia Read, Med. Ed., Alta Bates Hosp., 3001 Colby St., Berkeley 94705. (415) 845-7110, ext. 2055.

November 10-11—**Practical Nephrology for the Primary Care Physician.** UCLA. Saturday-Sunday.

November 15-16—**Neurology Update.** UCSD at Vacation Village, San Diego. Thursday-Friday.

November 15-17—**Advanced Cardiopulmonary Care.** PMC at Holiday Inn-Financial District/Presbyterian Hospital, San Francisco. Thursday-Saturday. 12 hrs. lecture; 18 hrs. lecture and workshop. $150 for lecture; $235, lecture and workshop.

November 29-December 1—**Infectious Disease Conference.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday.

December 1-2—**Practical Endocrinology for Primary Care Physicians.** UCLA. Saturday-Sunday.

December 6-7—**5th Annual Lyman A. Brewer, III, Cardiothoracic Symposium—The Esophagus.** White Memorial Medical Center at Bonaventure Hotel, Los Angeles. Thursday-Friday. Contact: Dir., Dept. of CME, White Memorial Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 263-6100 or (213) 268-5000.

December 6-9—**Neurotology Workshop.** PMC at Ilikai Hotel, Honolulu. Thursday-Sunday. 24 hrs. $435.

December 7-8—**Allergy/Immunology, Infectious Diseases, Endocrinology/Metabolism, Oncology.** American College of Physicians at San Francisco. Friday-Saturday. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200.

December 7-9—**Advances in Heart Disease 1980—12th Annual Seminar on Clinical Cardiology.** American College of Cardiology at Fairmont Hotel, San Francisco. Friday-Sunday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

December 12—**Management of Hypertension.** LLU. Wednesday. 4 hrs.

OBSTETRICS AND GYNECOLOGY

August 25-31—**Edward Tyler Symposium on the Practical Management of the Infertile Couple—3rd Annual.** Tyler Medical Clinic, Los Angeles, and Univ. of Hawaii School of Medicine at Maui Surf Hotel, Maui, Hawaii. One week. 16 hrs. $200. Contact: Jetset Tours, 2029 Century Park East, Suite 2130, Los Angeles 90067.

October 4-6—**Update in Obstetrics.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Saturday. 14 hrs. $175.

November 5-8—**Perinatal Medicine: State of the Art—1979.** UCSD at Vacation Village, San Diego. Monday-Thursday.

November 9-11—**Peripartum Period.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Friday-Sunday. 6 hrs. $150. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 29-December 1—**High-Risk Pregnancy—3rd Annual Conference.** Memorial Hospital Medical Center-UCI Center for Health Education at Canyon Hotel, Palm Springs. Thursday-Saturday. 18 hrs. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 6-8—**Gynecologic Urology: Theory and Practice, Basic and Advanced.** Memorial Hospital Medical Center-UCI Center for Health Education at Sheraton-Universal, Hollywood. Thursday-Saturday. 20 hrs. $300. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 7-8—**Adolescent Sexuality and Gynecology.** PMC. Friday-Saturday. 9 hrs. $125.

PEDIATRICS

September 19-20—**36th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Hilton Hotel, Los Angeles. Wednesday-Thursday. Contact: LAPS, P.O. Box 2022, Inglewood 90305.

September 28-29—**Practical Pediatrics With Doctor Sydney Gellis.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 9 hrs. $80.

October 13-18—**American Academy of Pediatrics—Annual Meeting.** Hilton Hotel and Brooks Hall, San Francisco. One week. 33-36 hrs. $60, members; $120, nonmembers. Contact: W. G. Janzen, Meeting Mgr., AAP, 1801 Hinman Ave., Evanston, IL 60204. (312) 869-4255.

November 12-14—**Primary Care Pediatrics.** UCI at Marriott Inn, Newport Beach. Monday-Wednesday. 17 hrs.

November 16-19—**Las Vegas Seminars.** American Academy of Pediatrics, Calif. Chapters 1, 2, 3, at Hilton Hotel, Las Vegas. Friday-Monday. $175, members; $200, nonmembers. Contact: AAP, Chap. 2, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

November 26-29—**Developmentally Disabled Child.** UCSD at Vacation Village, San Diego. Monday-Thursday.

PSYCHIATRY

September 10—**Ambulatory Treatment of the Depressed Patient.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

September 15—**Psychopharmacology in Clinical Practice: A Practicum in Mind-Allergy Drugs.** UCLA. Saturday.

October 5—**Interviewing Skills in Psychiatry.** PMC at Sacramento. Friday. 4 hrs. $25.

October 12-14—**Infant Psychiatry II.** UCSF. Friday-Sunday.

October 13—**Explorations of Healing in Psychotherapy.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 6 hrs. $60.

October 26—**Interviewing Skills in Psychiatry.** PMC at Los Angeles. Friday. 4 hrs. $25.

October 27—**Psychiatry Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 7 hrs. Contact: Prog. Coordinator, UCI Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 28-31—**Academy of Psychosomatic Medicine—Annual Meeting.** Fairmont Hotel, San Francisco. Sunday-Wednesday. Contact: Thomas C. Nelson, Exec. Dir., 70 W. Hubbard, Suite 202, Chicago, IL 60610. (312) 644-2623.

November 3—**Interviewing Skills in Psychiatry.** PMC. Saturday. 4 hrs. $25.

November 16—**Interviewing Skills in Psychiatry.** PMC at San Diego. Friday. 4 hrs. $25.

December 14—**Interviewing Skills in Psychiatry.** PMC at Anaheim. Friday. 4 hrs. $25.

RADIOLOGY AND PATHOLOGY

September 8-15—**Diagnostic Radiology: An In-Depth Seminar Approach to Selected Topics in Diagnostic Imaging.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $290.

September 13-May 8—**L.A. Bone and Joint Clinico-Pathological-Radiological Correlation and Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. 2nd Thursday of each month. 3 hrs./session. Contact: Prog. Coord., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 80801. (213) 595-3811.

September 15—**Emergency Radiology—7th Annual Radiology Symposium.** Southern California Permanente Medical Group at Century Plaza Hotel, Los Angeles. Saturday. Contact: Catherine Andrews, Ed. and Research Dept., SCPMG, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4516.

October 13-21—**International Body Imaging Conference—4th Annual.** West Park Hospital, Canoga Park, at Royal Lahaina Hotel, Maui, Hawaii. 9 days. 30 hrs. $295. Contact: Conf. Sec., Imaging Conf., West Park Hosp., Dept. of Radiology, 22141 Roscoe Blvd., Canoga Park 91304.

October 18-20—**New Advances and Controversies in Neuroradiology.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. 17 hrs. $190.

October 18-21—**Society of Nuclear Medicine—4th Annual Western Regional Meeting.** See Medicine, October 18-21.

October 19-20—**Mycology Review** (a course for residents in dermatology and pathology). See Medicine, October 19-20.

November 2-4—**Radiology of the Gastrointestinal System (II).** American College of Radiology at San Francisco. Friday-Sunday. 15 hrs. $275. Contact: Maurice H. Trautz, Dir. of Ed., ACR, 6900 Wisconsin Ave., Chevy Chase, MD 20015. (301) 654-6900.

November 12-14—**Liquid Chromatography in Clinical Analysis.** UCSF at Golden Gateway Holiday Inn, San Francisco. Monday-Wednesday. 19 hrs. $200.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 23 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

August 20—**Fluid-Electrolyte Problems in the Surgical Patient.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

September 24—**Trauma—Auto and Motorcycle Patients.** See Emergency Medicine, September 24.

October 4-6—**Advances and Controversies in Vascular Surgery.** Cedars-Sinai Medical Center at Century Plaza Hotel, Los Angeles. Thursday-Saturday. 19 hrs. $195. Contact: Lore Kahane, Room 2049, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles 90048. (213) 855-5547.

October 6—**Update of Pediatric Opthalmology.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $85. Contact: Lu Hendricks, Jules Stein Eye Inst., UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

October 11-13—**Surface Replacement of the Hip.** UCLA. Thursday- Saturday.

October 19-20—**Cataract Surgery Pragmatics.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 16 hrs. $175. Contact: Program Coordinator. Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 585-3811.

October 28-November 9—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200, otolaryngologists; $900, residents. Contact: Antonio De La Cruz, MD, Ear Research Inst., 256 S. Lake St., Los Angeles 90057.

November 5-9—**American Academy of Ophthalmology.** Civic Auditorium, San Francisco. Monday-Friday. Contact: Faye Anderson, Dir. of Mtgs., P.O. Box 7424, San Francisco 94120. (415) 563-5725.

November 24-December 1—**International Seminar on Operative Arthroscopy.** UCLA at Kauai, Hawaii. One week. 39 hrs. $650, with laboratories; $450 without laboratories.

December 6-8—**Trauma.** No. Calif. Chap. Committee on Trauma of the American College of Surgeons at Claremont Resort Hotel, Oakland. Thursday-Saturday. Contact: F. William Blaisdell, MD, Dept. of Surg., UCD Sch. of Med., Rm. 257, 4301 X St., Sacramento 95817. (916) 453-2207.

December 6-8—**Gynecologic Urology.** See Obstetrics and Gynecology, December 6-8.

December 8—**Blepharoplasty and Other Cosmetic Surgery of the Eyelid.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

December 6-9—**Neurotology Workshop.** See Medicine, December 6-9.

OF INTEREST TO ALL PHYSICIANS

August 19-24—**Family Practice Refresher Course—7th Annual.** UCD at Del Monte Hyatt, Monterey. One week. 30 hrs. $225.

PACIFIC MEDICAL CENTER

Course Offerings August-December, 1979

AUGUST 18
Strabismus

SEPTEMBER 10-13
EKG Self Assessment

SEPTEMBER 20
Transfusion Therapy in Clinical Practice

*OCTOBER 5
Interviewing Skills in Psychiatry I

OCTOBER 6
Allergy in Office Practice

NOVEMBER 9
Treatment of Venous and Thromboembolic Disease

NOVEMBER 15-17
Advanced Cardiopulmonary Care

DECEMBER 6-9
Neurotology Workshop

DECEMBER 7-8
Medical Knowledge Self Assessment Test I

DECEMBER 7-8
Adolescent Sexuality & Gynecology

*This course will be repeated at varying locations on October 26, November 3, November 16, and December 14

For further information write:
Continuing Education
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Tel. (415) 563-4321 Ext 2761

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August 25-31—**Edward Tyler Symposium on the Practical Management of the Infertile Couple—3rd Annual.** See Obstetrics and Gynecology, August 25-31.

August 28-October 16—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. Tuesdays; 8-10 p.m.

September 1-8—**Manipulation, Mobilization and Related Techniques in the Treatment of Musculo-Skeletal and Myofascial Pain Syndromes.** USC at Sheraton Waikiki Hotel, Hawaii. One week. 27½ hrs. $325.

September 9-13—**American Academy for Cerebral Palsy and Developmental Medicine—Annual Meeting.** St. Francis Hotel, San Francisco. Sunday-Thursday. 26 hrs. $95. Contact: Helen Bryan, Assoc. Exec. Dir., 1255 New Hampshire Ave. NW, #1030, Washington, DC 20036. (202) 659-8251.

September 12—**Workshop on Aging.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 6 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Memorial Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 284.

September 13-14—**Long Term Care Programs for the Elderly.** UCLA at Biltmore Hotel, Los Angeles. Thursday-Friday.

September 14-15—**The Last Horizon: Practical Solutions to Improved Patient Care of Patients with Terminal Illness.** UCD at Mansion Inn, Sacramento. Friday-Saturday. 15 hrs.

September 14-16—**Holistic Medicine.** Psychosomatic Medicine Clinic, Berkeley; American Holistic Medical Assn.; Symposia Medicus, Walnut Creek, at Biltmore Hotel, Santa Barbara. Friday-Sunday. 12 hrs. $185. Contact: Symposia Medicus, 2815 Mitchell Dr., No. 116, Walnut Creek 94598. (415) 935-7889.

September 15—**Psychopharmacology in Clinical Practice: A Practicum in Mind-Allergy Drugs.** See Psychiatry, September 15.

September 20—**California Venereal Disease Controllers' Clinical Session.** CMA Task Force on Venereal Disease, Calif. VD Controllers Assn. and Calif. Academy of Preventive Medicine at San Mateo. Thursday. Contact: Karin McGhee, CMA.

September 20—**Transfusion Therapy in Clinical Practice.** PMC and Irwin Memorial Blood Bank. Thursday. 6 hrs. $85.

September 23-28—**Stress: Harnessing Its Energy for Health.** UCD at Esalen Institute, Big Sur. Sunday-Friday. 30 hrs. $550.

October 8-12—**American Medical Association—Regional Meeting.** Ilikai Hotel, Honolulu. Monday-Friday. Contact: J. Kelso, AMA, 535 N. Dearborn St., Chicago 60610.

October 8-12—**Hawaii Medical Association.** Ilikai Hotel, Honolulu. Monday-Friday. Contact: J. Won, Exec. Dir., HMA, 320 Ward Ave., Suite 200, Honolulu 96814.

October 11-13—**Western Occupational Medical Association.** Monterey. Thursday-Saturday. Contact: B. H. Bravinder, P.O. Box 201, Alamo 94507.

October 13-21—**International Body Imaging Conference—4th Annual.** West Park Hospital at Royal Lahaina Hotel, Maui, Hawaii. 9 days. 30 hrs. $295. Contact: Conference Sec., Imaging Conf., West Park Hospital, Dept. of Radiology, 22141 Roscoe Blvd., Canoga Park 91304.

October 14-15—**Advances in Alcoholism Symposium.** UCSD and Raleigh Hills Foundation at Newporter Inn, Newport Beach. Sunday-Monday. 14 hrs. $150. Contact: Robert E. Schmitz, MD, Raleigh Hills Fnd., 881 Dover Dr., No. 20, Newport Beach 92663. (714) 645-4310.

October 28-31—**California Academy of Family Physicians—Annual Scientific Assembly.** Masonic Auditorium, San Francisco. Sunday-Wednesday. Contact: CAFP, 9 First St., San Francisco 94105. (415) 982-6091.

November 1-3—**Postgraduate Institute on Human Sexuality.** CMA, UCD, UCLA, UCSF, UCSD, UCI at Erawan Gardens, Indian Wells. Contact: Charlotte Newhart, CMA.

November 3—**Exercise: Health Hazards and Benefits.** UCLA. Saturday. 5½ hrs. $85.

November 4-7—**Southern Medical Association.** MGM Grand Hotel, Las Vegas. Sunday-Wednesday. In addition to 21 SMA programs, 22 postgraduate courses presented by AMA's Council on Cont. Physician Ed. Contact: SMA, 2601 Highland Ave., Birmingham, AL 35205.

November 5-9—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $290.

November 12-17—**American Society of Clinical Hypnosis—22nd Annual Scientific Meeting and Workshops.** San Francisco. Monday-Saturday. 40 hrs. $75, scientific program; $250, workshops. Contact: William F. Hoffman, Jr., Exec. Dir., 2400 E. Devon Ave., Suite 218, Des Plaines, IL 60018.

November 14—**Antibiotics.** LLU. Wednesday. 4 hrs.

November 26-30—**Postgraduate Institute for Primary Care Physicians.** UCSD at Hilton Hotel, San Diego. Monday-Friday. 40 hrs.

November 30—**The Many Faces of Shock—1979.** Daniel Freeman Hospital at Hyatt House, Los Angeles. Friday. 6 hrs. $90. Contact: Donald A. Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Hosp., 333 N. Prairie Ave., Inglewood 90301. (213) 674-7050.

December 5-7—**Prevention in Primary Care.** UCSD at Vacation Village, San Diego.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland, OR 97227. (503) 280-3200.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

February 25-29—**Eleventh Annual Family Practice Review.** Portland, Monday-Friday. Marriott Hotel. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OBSTETRICS AND GYNECOLOGY

October 22-24—**Third Annual Pacific Northwest Review of Obstetrics and Gynecology.** Portland, Monday-Wednesday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

SURGERY

December 7-8—**Recent Advances in Surgery.** Portland, Friday-Saturday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OF INTEREST TO ALL PHYSICIANS

August 17-18—**John Tomlin Memorial Cancer Lectures.** Medford, Friday-Saturday. Rogue Valley Country Club. Contact: American Cancer Society, Jackson County Unit, PO Box 698, Medford, OR 97501. (503) 779-6091.

September 14-15—**Newer Concepts in Cardiology.** Ashland, Friday-Saturday. Ashland Hills Motel. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

September 28-29—**Shaw Memorial Lectures on Geriatric Health Care.** Portland, Friday-Saturday. OMA Headquarters. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

October 4-5—**Understanding Human Sexuality: Current Assessment and Treatment Approaches.** Portland, Thursday-Friday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

November 16-17—**Sixth Annual Symposium on Critical Care Medicine.** Portland, Friday-Saturday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

January 25-27—**Seminars in Cardiology.** Portland, Friday-Sunday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 16-20—**American College of Physicians Review Course.** Portland, Monday-Friday. Jantzen Beach Thunderbird. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 25-27—**Symposium on Sports Medicine.** Eugene, Wednesday-Friday. Thunderbird Motor Inn. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

August 16-18—**Controversies in Otolaryngology.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

September 17-21—**Advances in Family Practice.** Seattle. Monday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

September 20-23—**Radiology Northwest III.** Seattle. Thursday-Sunday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

September 23-24—**Medical Problems in the Surgical Patient.** Walla Walla. Sunday-Tuesday. Walla Walla General Hospital. Contact: Sharon Werner, Walla Walla General Hospital, 933 Bonsella, Walla Walla, WA 99362. (509) 522-0480, Ext. 543.

September 27-29—**Plastic Surgery Repair for Primary MDs.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

October 5-6—**Scientific Program, Annual Meeting, Washington State Medical Association.** Seattle. Friday-Saturday. Washington Plaza Hotel. Contact: Mr. George Morford, Washington State Medical Association, 2033 Sixth Avenue, Seattle, WA. (206) 623-4801.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: 1980—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 23-27, 1980, Registry Resort, Scottsdale.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: February 7-13, 1980, Town and Country, San Diego.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 19-23, 1979, the Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 8-12, 1979, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual meeting: 1980—date and place to be announced.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 11-13, 1979, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 16-18, 1980, MGM Grand, Las Vegas.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: 1980—date and place to be announced.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Meeting: November 2-4, 1979, OMA Headquarters.

Utah State Medical Association—42 S. 5th East St., Salt Lake City 84102. Annual Meeting: September 11-14, 1979, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 4-7, 1979, Washington Plaza Hotel, Seattle.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: August 28-31, 1979, Jackson Lake Lodge, Moran.

November 15-16—**Critically Ill Surgical Patient.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 28-29—**Northwest Stroke Symposium.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: Education and Training Department, Northwest Hospital, 1551 North 120th, Seattle, WA 98133. (206) 364-0500, ext. 686.

ALASKA, MONTANA AND IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

August 29—**Dysplasia and Early Cervical Neoplasia**—Univ. of Wash. OB-GYN Sessions (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

MONTANA

September 7-8—**Montana/Wyoming Chapter, American College of Physicians' Regional Meeting**—Fairmont Hot Springs, Friday-Saturday. Contact: J. E. McGreevey, MD, 401 S. Alabama, Butte, MT 59701. (406) 723-4384.

October 5-6—**American Cancer Society (Montana Chapter) Annual Meeting.** Billings. Friday-Saturday. Northern Hotel. Contact: Ruth Eaton, 2820 1st Ave. S., Billings, MT 59101.

October 11-13—**Montana Medical Association Annual Meeting.** Kalispell. Thursday-Saturday. Outlaw Inn. Contact: Montana Medical Association, 2021 Eleventh Ave., Suite 12, Helena, MT 59601. (406) 443-4000.

Index to
The Western Journal of Medicine Advertising

AMA REGIONAL CME MEETING 20
BANK OF AMERICA
Business Services 29
BOEHRINGER INGELHEIM LTD.
Catapres 7, 8, 9, 10
BURROUGHS WELLCOME CO.
Zyloprim 19
CALIFORNIA MEDICAL ASSOCIATION
1979 Postgraduate Institute—Human Sexuality 31
CEDARS-SINAI MEDICAL CENTER
Advances and Controversies in Vascular Surgery 20
CLASSIFIED 26, 28, 30
DOCTORS' COMPANY, THE 23
ELI LILLY AND COMPANY
V-Cillin K 6
FIRSTMARK CAPITAL CORPORATION 20
GRUNE & STRATTON PUBLISHERS 35
MEAD JOHNSON PHARMACEUTICAL DIVISION
Colace 17
Quibron 18
MERCK SHARP & DOHME
Aldomet 2
ORTHO PHARMACEUTICALS
Monistat IV 12, 13, 14
PACIFIC MEDICAL CENTER
Course Offerings August-December, 1979 35
PHARMACEUTICAL MANUFACTURERS ASSOCIATION 24, 25
PRESTO FOOD PRODUCTS, INC.
Mocha Mix 11
ROCHE LABORATORIES
Gantanol ..... 2nd Cover, 1, 2
Valium ..... 3rd & 4th Covers
SANDOZ PHARMACEUTICALS
Hydergine 15
SMITH KLINE & FRENCH COMPANY
Tagamet 3
E. R. SQUIBB & SONS INC.
Pronestyl 21, 22
UNIVERSITY MICROFILMS INTERNATIONAL 27
UPJOHN COMPANY, THE
Motrin 5

THE WESTERN Journal of Medicine

VOLUME 131 • NUMBER 3 **SEPTEMBER 1979**

179 *Nontraditional Problems of Antihypertensive Management* PETER RUDD, MD, and KEITH I. MARTON, MD

193 *Amyloidosis and Periodic Peritonitis (Familial Mediterranean Fever)*
FARHAN BAKIR, MB, ChB, MS(Med), FRCP; M. MURTADHA, MB, ChB, MS(Med), MRCP, and NAHLA ISSA, MB, ChB

196 *Candida Pneumonia—Experience With 20 Patients*
ZAB MOHSENIFAR, MD; SAWTANTRA K. CHOPRA, MD; B. LAMAR JOHNSON, JR, MD, and DANIEL H. SIMMONS, MD, PhD

201 *Prenatal Diagnosis by Amniocentesis in 800 Pregnancies*
MIRIAM G. WILSON, MD; JUNE A. GILMAN, MS, and BONNIE KELLOGG, MS

MEDICAL PROGRESS

205 *The Relationship Between Genetics and Environment in the Pathogenesis of Rheumatic Diseases*
ANDREI CALIN, MD, MRCP

SPECIALTY CONFERENCE

219 *Factitious Disease in Pediatrics*
Participants: MARTIN STEIN, MD; F. BRUDER STAPLETON, MD; DEBORAH RUFNER, MD; DAVID K. EDWARDS, MD, and WILLIAM L. NYHAN, MD, PhD
Departments of Pediatrics and Radiology, University of California, San Diego, School of Medicine, University of California Medical Center, San Diego, and U.S. Naval Regional Medical Center, San Diego

MEDICAL STAFF CONFERENCE

225 *Asbestos-Related Lung Disease* Chief Discussant: JEFFREY A. GOLDEN, MD

IMPORTANT ADVANCES IN CLINICAL MEDICINE

231 *Anesthesiology—Epitomes of Progress*

EDITORIALS

239 • *The Accreditation of Continuing Medical Education* • *New Perspectives in the Treatment of Hypertensive Patients* • *A New Kind of Melting Pot* • *Rheumatic Disease—A Case of the Soil and the Seed*

CASE REPORTS

244 *Myoglobinuric Acute Renal Failure Associated With Phencyclidine Abuse*
RAMAN PATEL, MD; ALI ANSARI, PhD, and JOHN I. HUGHES, MD

247 *Malignant Pseudomonas External Otitis*
JOHN E. EDWARDS, JR, MD; WILLIAM A. COMBS, MD, and LUCIEN B. GUZE, MD

CORRESPONDENCE

251 • *Techniques in Treatment of Retained Gallstones* • *Another View of Functional Overlay* • *Organized Medicine as 'My Doctor'* • *An Incorrect Reference*

INFORMATION

256 *Generic Screening—A Systems Approach to Patient Care Audit Studies*
SAMUEL R. SHERMAN, MD

258 *Tamoxifen in the Management of Metastatic Cancer of the Breast*
LAWRENCE A. CONE, MD; NEIL E. ROMANOFF, MD, and NICOLA A. HELM, RN

Books Received, See Advertising Page 23

★ CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII; OREGON; WASHINGTON; ALASKA, MONTANA AND IDAHO
(See Advertising Page 28)

★★ Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association and the Washington State Medical Association

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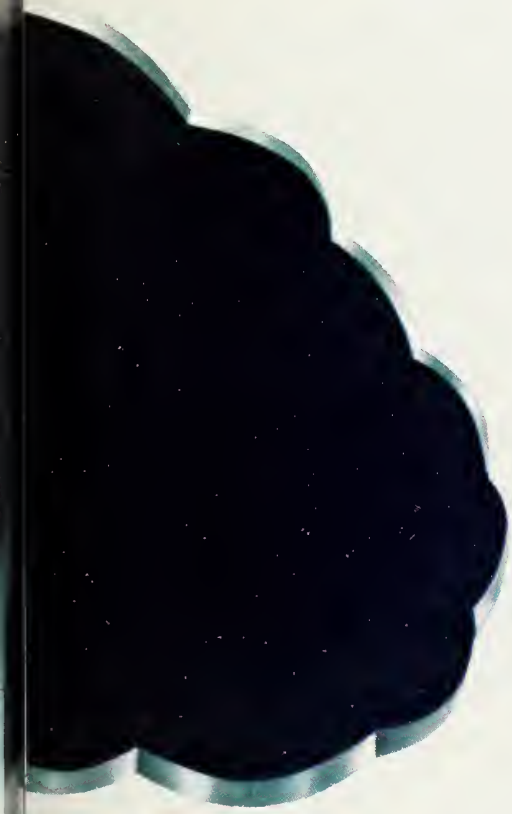

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LIBRAX®

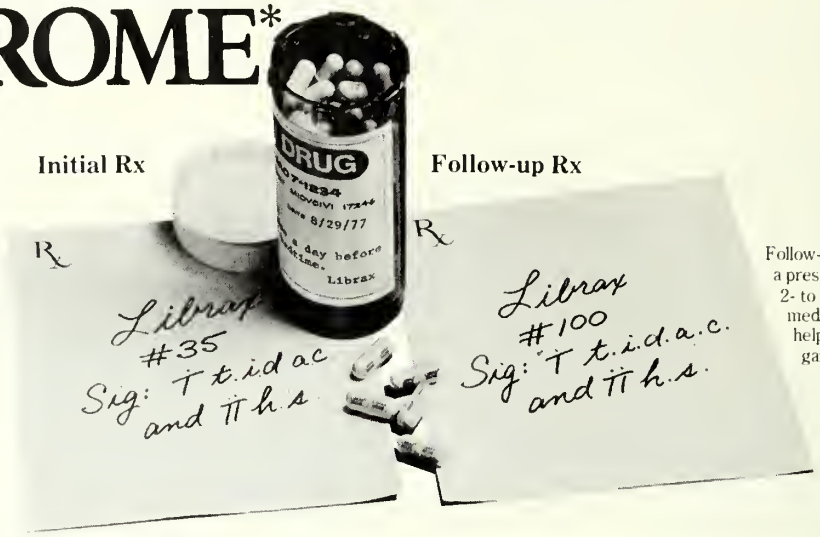
Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

A distinct advantage for patients with irritable bowel syndrome

ROCHE

*Librax has been evaluated as possibly effective for this indication. Please see brief summary of prescribing information on following page.

A DISTINCT ADVANTAGE FOR PATIENTS WITH IRRITABLE BOWEL SYNDROME*



Initial Rx

The initial prescription allows evaluation of patient response to therapy.

Follow-up Rx

Follow-up therapy with a prescription for a 2- to 3-week supply of medication usually helps maintain patient gains.

Adjunctive

LIBRAX®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

antianxiety/antispasmodic/antimotility

Please consult complete prescribing information, a summary of which follows:

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl/Roche) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

How Supplied: Available in green capsules, each containing 5 mg chlordiazepoxide HCl (Librium®) and 2.5 mg clidinium Br (Quarzan®)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.

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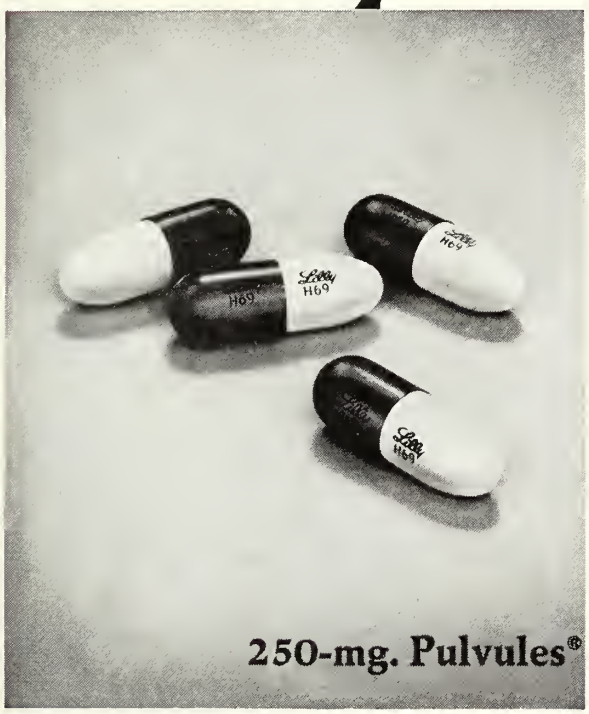

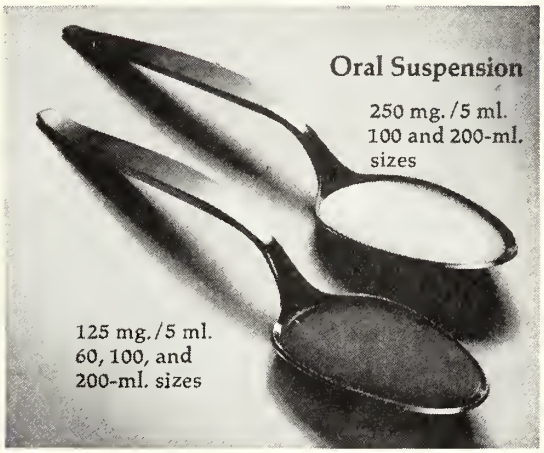

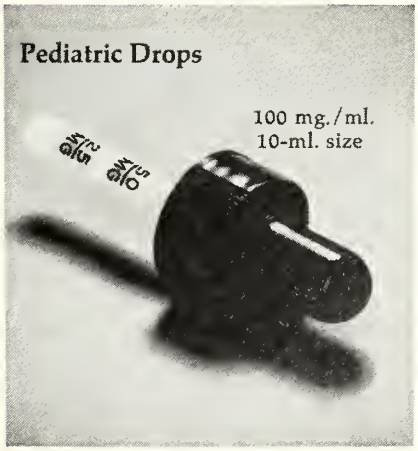

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Psoriasis (23 patients); 96% improved[7]
Psoriasis (49 patients); 96% improved[9] (with overnight occlusion)
Eczematoid Dermatitis, Atopic Dermatitis, Psoriasis, Neurodermatitis (47 patients); 98% improved[4]
Psoriasis (60 pts.); 95% improved[14]
Neurodermatitis, Atopic Dermatitis, Psoriasis, Eczematoid Dermatitis (59 patients); 98% improved[5]
Psoriasis (50 patients); 96% improved[15]
Atopic Dermatitis, Psoriasis, Neurodermatitis, Eczematoid Dermatitis (457 patients); 96% improved[6]
Psoriasis (105 patients); 100% improved[17]
Eczematoid Dermatitis, Psoriasis (110 patients—12 eczematoid and 17 psoriasis cases had occlusive dressings); 98% improved[8]
Atopic Dermatitis, Eczematoid Dermatitis, Psoriasis (27 patients); 88% improved[11]
Eczematoid Dermatitis, Psoriasis (392 patients); 96% improved[10]
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REFERENCES

1. Baiocchi O: Jornal Brasileiro de Ginecologia, September, 1973
2. Leibsohn E, Bagatell FK: Brit J Derm 90:435-440, 1974
3. Reinhard W, Weber G, Petres J: Zeitschrift für Hautkrankheiten, April, 1974
4. Jonquieres EDL, Favere M, Pasut H: La Semana Médica 144:447-449, 1974
5. Cordero A: La Semana Médica 145:145-148, 1974
6. Bagatell FK: Cutis 14:459-462, 1974
7. Lepaw MI: Scientific Exhibit presented at Dec., 1974, meeting of American Academy of Dermatology, Chicago, IL
8. Theodorides A, Stratigos I, Vareltsides A, et al: Iatrikā Chronikā 14:559-574, 1974
9. Clark RF, Clement ER: Arch Derm 111:731-733, 1975
10. Sudilovsky A, Clewe TH: Clin Pharmacol 15:779-784, 1975
11. Turnbull BC: Aust J Derm 16:17-19, 1975
12. Bleeker J: Curr Med Res Opinion 3:225-228, 1975
13. Savin RC: J Int Med Res 4:34-36, 1976
14. Kanof NB, Blau S: Cutis 17:796-798, 1976
15. Close JE: Int J Derm 15:534-537, 1976
16. Lepaw MI: Cutis 21:571-573, 1978
17. Savin RC: Dermatology 1:34-38, 1978
18-21. Data on file at Squibb Institute for Medical Research

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CONTRAINDICATION: Topical steroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparations.
PRECAUTIONS: ***General***—If irritation develops, discontinue the product and institute appropriate therapy. In presence of an infection, institute use of a suitable antibacterial or antifungal agent. If a favorable response does not occur promptly, discontinue the corticosteroid until the infection has been adequately controlled. If extensive areas are treated or if the occlusive technique is used, there will be increased systemic absorption of the corticosteroid and suitable precautions should be taken, particularly in children and infants. These preparations are not for ophthalmic use.
Usage in Pregnancy—Although topical steroids have not been reported to have an adverse effect on human pregnancy, the safety of their use in pregnant women has not been absolutely established. In laboratory animals, increases in incidence of fetal abnormalities have been associated with exposure of gestating females to topical corticosteroids—in some cases at rather low dosage levels. Therefore, drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.
Occlusive Dressing Technique—The use of occlusive dressing increases the percutaneous absorption of corticosteroids. For patients with extensive lesions it may be preferable to use a sequential approach, occluding one portion of the body at a time. Keep the patient under close observation if treated with the occlusive technique over large areas and over a considerable period of time. Occasionally, a patient who has been on prolonged therapy, especially occlusive therapy, may develop symptoms of steroid withdrawal when the medication is stopped. Thermal homeostasis may be impaired if large areas of the body are covered. Discontinue use of the occlusive dressing if elevation of the body temperature occurs. Occasionally, a patient may develop a sensitivity reaction to a particular occlusive dressing material or adhesive and a substitute material may be necessary. If infection develops, discontinue the use of the occlusive dressing and institute appropriate antimicrobial therapy.
ADVERSE REACTIONS: The following local adverse reactions have been reported with topical corticosteroids, especially under occlusive dressings: burning sensations, itching, irritation, dryness, folliculitis, hypertrichosis, acneform eruptions, perioral dermatitis, allergic contact dermatitis, hypopigmentation, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.
For full prescribing information, consult package inserts.
HOW SUPPLIED: 0.025% Cream in tubes of 15 g and 60 g and in jars of 240 g (8 oz); 0.1% Cream in tubes of 15 g, 30 g, and 60 g and in jars of 240 g (8 oz); 0.025% Ointment in tubes of 15 g and 60 g and in jars of 240 g (8 oz); 0.1% Ointment in tubes of 15 g, 30 g, and 60 g and in jars of 240 g (8 oz); 0.1% Solution in plastic squeeze bottles of 20 ml and 60 ml.

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Each 1 mg Hydergine tablet contains dihydroergocornine mesylate 0.333 mg, dihydroergocristine mesylate 0.333 mg, and dihydroergocryptine (dihydro-alpha-ergocryptine and dihydro-beta-ergocryptine in the proportion of 2:1) mesylate 0.333 mg, representing a total of 1 mg.

They're in their late sixties, the beneficiaries of more liberal retirement laws and more enlightened attitudes toward the elderly. They're leading socially productive lives. But recently, without any clear cause, they had each begun to experience mild episodes of symptoms such as confusion, mood-depression, and dizziness. Their ability to function could have been jeopardized. That's when they became the beneficiaries of oral Hydergine therapy.

The still-functioning geriatric can benefit from Hydergine treatment

It is quite common for cognitive and emotional symptoms of deterioration to manifest gradually in the elderly. During this early stage, such symptoms are mild and more amenable to treatment. It is at this stage that Hydergine therapy has proved most effective. Patients tend to respond better, and with symptoms effectively relieved—or at least their progression retarded—the ability to function can be maintained.

Oral Hydergine tablets promote better patient compliance

Compared with the sublingual form, dosage administration is easier, with less need for supervision.

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Contraindications: Hypersensitivity to the drug.
Precautions: *Because the target symptoms are of unknown etiology, careful diagnosis should be attempted before prescribing Hydergine tablets and sublingual tablets.*
Adverse Reactions: Serious side effects have not been found. Some sublingual irritation, transient nausea, and gastric disturbances have been reported. Hydergine tablets and sublingual tablets do not possess the vasoconstrictor properties of natural ergot alkaloids.
Dosage and Administration: 1 mg three times daily. Alleviation of symptoms is usually gradual and results may not be observed for 3–4 weeks.
How Supplied: Hydergine tablets (for oral use) 1 mg, packages of 100 and 500. **Hydergine sublingual tablets 1 mg,** containing dihydroergocornine mesylate 0.333 mg, dihydroergocristine mesylate 0.333 mg, and dihydroergocryptine (dihydro-alpha-ergocryptine and dihydro-beta-ergocryptine in the proportion of 2:1) mesylate 0.333 mg, representing a total of 1 mg; packages of 100, 500, and 1000. **Hydergine sublingual tablets 0.5 mg,** containing dihydroergocornine mesylate 0.167 mg, dihydroergocristine mesylate 0.167 mg, and dihydroergocryptine (dihydro-alpha-ergocryptine and dihydro-beta-ergocryptine in the proportion of 2:1) mesylate 0.167 mg, representing a total of 0.5 mg; packages of 100 and 1000.
Before prescribing, see package insert for full product information.

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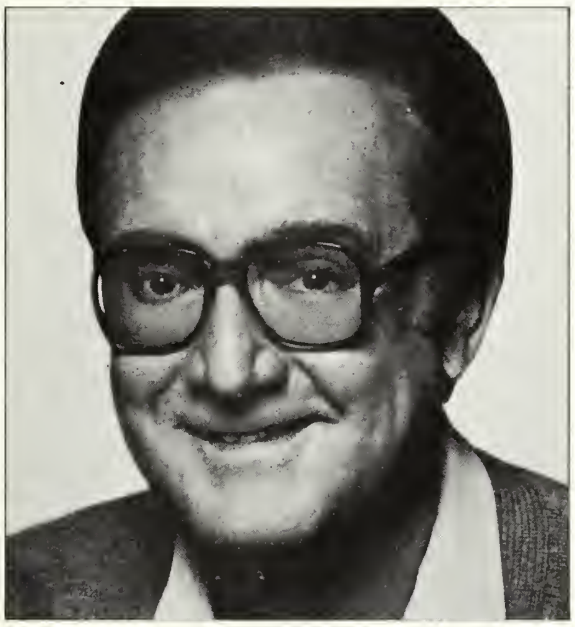

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Portion Size 1 Fluid Ounce (2 Tbs.)

Servings Per Container	16
Calories	40
Protein	0 grams
Carbohydrate	3 grams
Fat	3 grams
Percent of Calories from Fat	73%
Polyunsaturated Fat	1 gram
Saturated Fat	0 grams
Cholesterol (Δ) (0 mg/100g)	0 mg

Percentage of U S Recommended Daily Allowance (U S RDA)*
*Contains less than 2% of the U S RDA of Protein, Vitamin A, Vitamin C, Thiamine, Riboflavin, Niacin, Calcium, Iron.
Δ Information on fat and cholesterol content is provided for individuals who, on the advice of a physician, are modifying their total dietary intake of fat and cholesterol

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PERCOCET®-5 Tablets (II)

Brief Summary of Prescribing Information

DESCRIPTION Each tablet of PERCOCET®-5 contains 5 mg oxycodone hydrochloride (WARNING: May be habit forming), 325 mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS. 6085 BS

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Tablets

PERCOCET®-5

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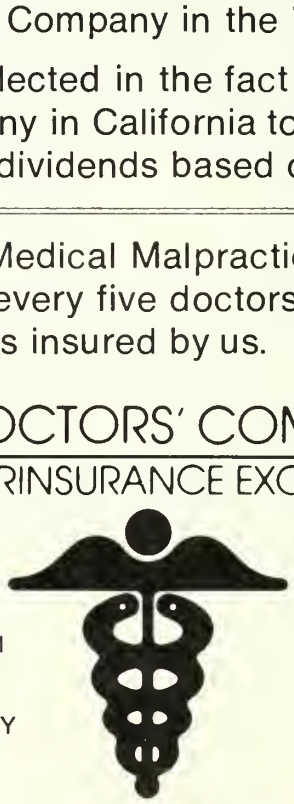

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Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.
Vasodilan injection, isoxsuprine HCl, 5 mg., per ml.

Dosage and Administration: Oral: 10 to 20 mg., three or four times daily.
Intramuscular: 5 to 10 mg. (1 or 2 ml.) two or three times daily. Intramuscular administration may be used initially in severe or acute conditions.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.
Parenteral administration is not recommended in the presence of hypotension or tachycardia.
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Adverse Reactions: On rare occasions oral administration of the drug has been associated in time with the occurrence of hypotension, tachycardia, nausea, vomiting, dizziness, abdominal distress, and severe rash. If rash appears the drug should be discontinued.
Although available evidence suggests a temporal association of these reactions with isoxsuprine, a causal relationship can be neither confirmed nor refuted.
Administration of single dose of 10 mg. intramuscularly may result in hypotension and tachycardia. These symptoms are more pronounced in higher doses. For these reasons single intramuscular doses exceeding 10 mg. are not recommended. Repeated administration of 5 to 10 mg. intramuscularly at suitable intervals may be employed.

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THE WESTERN
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Refer to: Rudd P, Marton KI: Nontraditional problems of antihypertensive management. West J Med 131:179-192, Sep 1979

Nontraditional Problems of Antihypertensive Management

PETER RUDD, MD, *and* KEITH I. MARTON, MD, *Stanford, California*

Problems with patient screening, disease labeling, diagnosis confirmation, patient compliance and physician adherence continue to undermine efforts to control hypertension and prevent its complications.

Simple screening involves patient selection bias, limited new diagnosis, arterial pressure lability, ambiguous disease definition, complex measurement imprecision and deficient patient follow-through. Case finding may improve some of these deficiencies. Recent data suggest that labeling a person as hypertensive may produce impaired self-concept, marital dissatisfaction and absence from work. Newer series confirm the low prevalence of curable, secondary hypertension among unselected patients and strongly argue for restricting extensive hypertensive evaluations to selected subpopulations. Patient noncompliance is highly prevalent, poorly predicted and imprecisely measured. Based on successful trials, specific suggestions can be made to achieve maximum patient compliance and physician adherence to diagnostic and therapeutic guidelines.

AT FIRST GLANCE, the problem of hypertension may appear solved. Several published guidelines[1,2] give recommendations with a sense of great finality, as if one need only prescribe a few medications to resolve the problem. In reality, physicians have focused on selected components of the hypertensive constellation, clarifying a great deal of the uncertainty while conveniently ignoring several major issues.

Sackett's formulation[3] defines three major steps in reducing hypertension's morbidity and mortality: (1) hypertensive persons must be identified; (2) they must establish effective contact with clinical personnel so that workup, appropriate treatment and lifelong observation can be carried out, and (3) these hypertensive persons, once diagnosis and evaluation are done, must take their medication.

This formulation appears deceptively simple because the steps are obvious and logical. As Sackett emphasizes, success is achieved only if all steps are properly completed. Yet most hypertension biomedical research and scholarly reviews have paid little attention to failures in these steps. They have concentrated on pathogenetic mechanisms and risk factor analysis, disease prevalence and consequences, pharmacokinetics and medication sequences. They have highlighted plasma renin activity and adverse drug reactions while ignoring other critical issues.

This review deals with five such ignored issues:

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patient screening, disease labeling, diagnosis confirmation, patient compliance and physician adherence. While none of the topics is new, several recent studies offer important perspectives and insight, as the problem of hypertension receives increased national attention.

Patient Screening

All screening efforts basically search for preclinical or asymptomatic disease among a population at risk. Such efforts assume that a simple, inexpensive and mutually acceptable screening mechanism exists for patients and health professionals. The efforts further assume that the disease has some latent period in which intervention can halt, slow down or reverse the pathophysiologic change, and that the therapy produces a better outcome than no therapy at all.[4] By intentionally selecting asymptomatic target populations, screening distinguishes itself from case-finding efforts, which examine persons already receiving care for another condition—as when blood pressure is measured by an optometrist,[5] for example.

This distinction is not academic because it raises the issue of selection bias, the process by which misrepresentative proportions of diseased persons are detected because they differentially present for examination. Although all mass screening has shortcomings, at least six particular problems have been identified in screening programs to detect hypertension.

Poor Patient Turnout

First, only a small proportion of persons at risk (usually less than 20 percent) come to a central screening point, such as a shopping center, despite vigorous mass media and direct mailing campaigns.[6] More intense and systematic efforts, such as door-to-door screening, involve much higher costs in time and personnel.

Few New Cases

Patients frequently come to mass screening facilities to confirm their private physicians' findings or to reassure themselves that their antihypertensive therapy or lack of it remains appropriate. This reflects the second major problem with hypertensive screening: more than three fourths of the screened persons have already had their blood pressure taken in the preceding three years,[3] and a 1973 Harris Poll reported that three fourths had had blood pressure recordings in the

TABLE 1.—*Results of Varied Screening Efforts for Hypertension*

Study (Years)	*Sample Characteristics*	*Number Screened*	*Population at Risk (Percent)*	*Persons Termed Hypertensive* (Percent)*	*Persons with Previously Unknown Hypertension (Percent)*	*Hypertensive Persons Under Medication (Percent)*	*Hypertensive Persons Under Control (Percent)*	*Hypertensive Persons Unaware, Untreated or Uncontrolled (Percent)*
Baldwin County[6] (1962)	Rural; 4% black	3,084	NA	20	41	30	14	86
National Health Survey[6] (1960-1962)	Probability sample USA	6,672	NA	18	43	36	16	84
Alameda County[6] (1966)	Urban/Suburban	2,495	NA	17	NA	36	23	77
Atlanta Community HBP Program[6] (1970-1971)	Urban; black	6,012	26	23	27	45	17	83
Louisiana State University Survey[9] (1973)	Urban; 26% black	25,284	5	35	50	70	13	87
Charlottesville Blood Pressure Survey[10] (1974)	Urban	12,371	42	21	22	61	22	78
Montreal Hypertension Screening Project[7] (1977)	Urban	12,055	NA	19	37	38	25	75

HBP = high blood pressure NA = not available

*Prevalence equal to or greater than 160/95 mm of mercury or taking antihypertensive medication.

past 12 months.[7] Consequently, discoveries of previously unsuspected hypertension are rare. The screened population's age distribution determines the proportion of hypertensive cases found more than any other single factor.[8]

Table 1 reviews the experience of seven major hypertension screening efforts in the last 16 years. Although many persons were screened, no survey contacted even a simple majority of all local people at risk for hypertension. The prevalence of hypertension (defined as systolic blood pressure of at least 160 mm of mercury and diastolic blood pressure of at least 95 mm of mercury, or a history of taking antihypertensive medications) averaged 21.6 percent. Fewer than half the persons labeled hypertensive had been previously unaware of the diagnosis.

Unsustained Abnormality

A third problem involves the high prevalence of labile hypertension, which affects as many as 52 percent of patients with initially elevated blood pressure. It appears most commonly among patients 15 to 54 years old, with approximately equal distribution by race and sex.[10] Screened patients may justifiably complain about the cost, worry and inconvenience of blood pressure follow-up if they are needlessly referred to private physicians or clinics without some mechanism for confirming the elevated first determination. Many physicians in turn may complain about the extra effort to disprove and dismiss high readings during screening.

Limits of Abnormality

Commonly, community physicians complain that surveys use inflexible criteria for hypertension, without regard to a patient's age. Although most large-scale surveys have used a cutoff point of 160/95 mm of mercury to define hypertension with the range 140 to 159/90 to 94 mm of mercury *borderline* hypertension, these criteria are arbitrary. Epidemiologic studies report a continuum of risk extending from obviously elevated levels through the *normal* range, defying attempts to set a clear distinction between normal and abnormal. This fourth problem of exactly defining abnormality has been long recognized, even though Sokolow and co-workers[11] showed a good correlation between portable (in contrast to casual) blood pressure determinations and essential hypertensive complications. The implications of this problem to planning screening programs have become clearer, however, in recent studies. Alderman and Yano[12] noted that labile false-positive hypertension and overall prevalence could be reduced from 23 percent to 7 percent by using initial diastolic blood pressure of 105 or greater, rather than the traditional 160/95 criterion. Even more critical, Roistacher and associates[13] calculated that raising the minimal blood pressure necessary for treatment initiation from 140/90 to 160/95 mm of mercury decreased the number of patients treated by a third, the number of personnel used per patient by a fourth and the cost of drugs by a third. In exchange, the attack rate for morbid events among men increased by 14 percent. The age of difficult cost-benefit decisions has arrived, and perhaps hypertension should be defined as the blood pressure level above which investigation and treatment do more good than harm.[14] This critical level probably varies with age, sex, quality of available medical facilities and cultural norms of benefit versus harm. Yet faced with the complexities of making this definition operational, we retreat to simple, more arbitrary, definitions of normality.

Measurement Reliability and Validity

Even if there were general agreement on absolute, if somewhat arbitrary, hypertensive criteria, the fifth problem of reliability and validity of measurement would remain. Both biologic and operational variabilities complicate the measurement process. Blood pressure variability in different readings in the same person approximates half the real between-subject standard deviation for both systolic and diastolic pressures, even under careful conditions of measurement.[15] Using only single blood pressure measurements, surveyors and clinicians are likely to overestimate the real variation between subjects, misclassify both hypertensive and hypotensive persons and underestimate the strength of risk factor correlations.[14] A wide variety of systematic biases also exists, including interobserver variability,[16] casual versus basal conditions, especially involving the presence of a physician,[17] arm-cuff disproportion[18] and digit preference.[19] All sphygmomanometers underestimate systolic and overestimate diastolic blood pressure. Standard mercury manometers produce the least variability compared with direct intra-arterial measurement.[20]

While the morbidity of direct intra-arterial blood pressure measurement appears prohibitive for routine use, several studies have criticized the

reliability of casual readings. Sokolow and co-workers[11] consistently found casual clinic-based readings to be higher and less well correlated with hypertensive complications than patient-monitored, presumably basal readings. Ibrahim and colleagues[21] similarly found closer correlation between electrocardiographic changes in QRS voltage or ST-T segment and blood pressure measurements done at home than with casual office blood pressure readings. Irving and co-workers[17] reduced the disparity between casual and automatically recorded blood pressures by taking the mean of all casual readings. Even so, 40 percent of the casual readings exceeded the automated *basal* level by at least 10 percent. To obtain still closer approximation, Mathieu and associates[22] used a multiple linear regression equation to predict the fourth reading based on the first and second determinations. After establishing the coefficients for his own equation, a clinician should be able to predict basal blood pressure from two readings taken ten minutes apart. If above the normal range, the predicted basal blood pressure would classify the patient as hypertensive within 95 percent confidence limits. To facilitate the screening task and reduce observer bias, attention has shifted to automated devices. But their accuracy has not compared favorably with standard mercury manometers in published series,[23] although second-generation devices appear more promising.[24]

Loss to Follow-Up

The final but perhaps most important problem arising from mass screening or office case finding is the simple failure of many hypertensive people to seek follow-up care. Wilber and Barrow[6] documented that less than 50 percent of identified hypertensive persons consulted a physician or clinic as a result of their screening; only 42 percent of treated patients continued antihypertensive therapy for at least three to nine months and only 21 percent had blood pressure readings below 160/95 mm of mercury when surveyed again.

With such poor short-term outcome, one can readily understand reluctance to expend limited health resources on further mass screening without previous assurance of reducing screening's shortcomings. Several factors—selection bias of persons volunteering for screening, limited discovery of new cases, high prevalence of labile hypertension, ambiguity of hypertension definition, complexities of reliable and valid measurement, and low patient follow-up—all severely limit the successful use of mass screening for hypertension. Case finding offers the modest advantage of a more immediate link to sources of future medical care, but leaves unanswered the critical questions of what level of blood pressure is abnormal and how many cases need to be detected to decrease cardiovascular mortality significantly. While recent reports state that cardiovascular mortality has declined over the last ten years,[25] the decline began before publication of the Veterans Administration cooperative studies.[26,27] The sequence suggests that improved survival is unrelated to more aggressive and successful antihypertensive management by health professionals after the Veterans Administration's reports. Stason and Weinstein[28] categorically conclude that further screening expenditures cannot be justified unless treatment and medication compliance following screening improves.

Disease Labeling

Recently, another previously unsuspected issue has emerged to challenge screening efforts. Sackett and co-workers[29,30] described several negative consequences of labeling persons as hypertensive following screening. Using a stable, male, blue-collar, steelworker population,[31] the investigators screened a random sample of 5,400 workers and identified 230 untreated men with diastolic blood pressures that remained greater than 95 mm of mercury for three months. After referral to either private or work-site physicians for follow-up, 66 percent of the men ultimately began antihypertensive treatment.

Initially focusing on work absenteeism, the investigators noted that patients previously unaware of hypertension increased their average days of absenteeism more than threefold (2.7 to 8.4 days per year) and almost 1½ times that (6.1 days per year) of patients previously aware of hypertension (t-test, P less than 0.05). Remarkably, the mean absenteeism increase was greatest among patients previously unaware of their hypertension and lowest among untreated persons aware of their condition. Concerned that the increased absenteeism reflected hypertension-related events, the investigators observed that most of the increment reflected increase in the proportion of absenteeism episodes lasting more than ten days. Rise in absenteeism was associated with treatment, medication noncompliance and educational efforts among previously unaware hyper-

tensive persons, but was unrelated to ultimate control of blood pressure.

They tried to clarify the cause of increased absenteeism by using attitudinal questionnaires (self-concept, marital and personal satisfaction) immediately before labeling and one year after labeling persons as hypertensive.[30] Increases in absenteeism were correlated with deterioration in marital and home satisfaction as well as impaired self-concept (feelings of personal strength, independence and activity).

The authors concluded that such potential, negative consequences very likely detract from the overall benefit of hypertensive screening and therapy and attempts should be made to offset the psychosocial handicap which appears to follow labeling. Because the full details of these investigations have been published in abstract form only, thorough analysis of the studies' methodology and results is difficult. The implication that labeled persons learn to consider themselves more fragile and debilitated is provocative and potentially devastating to current screening efforts in a variety of settings and diseases. The study should be replicated, however, in varying settings with special attention to including women, many types of workers and a control group of normotensive workers in which the same screening techniques and questionnaires are used.

These psychosocial concerns may have to be added to the current list of negative consequences of screening which include more expensive or denied insurance coverage[32] and, occasionally, job discrimination. Special reassurance therapy may be needed at the time of screening to minimize any negative consequences of labeling.

Diagnosis Confirmation and Workup

Returning to Sackett's formulation for managing hypertension, it is important to establish effective links to long-term clinical care, after identifying a patient as hypertensive. The controversies surrounding diagnosis confirmation and workup are no less complex than the imperfections of screening. These controversies involve the particulars rather than the principles. Most clinicians would agree that persons found to be hypertensive at screening need confirmation of the diagnosis and, if it is confirmed, subsequent baseline evaluation, appropriate search for secondary causes of hypertension and education to motivate their compliance. Unfortunately, there are no data to evaluate the relative effectiveness of alternative workup approaches. In the absence of validated guidelines and without better data, one must consider patient discomfort and cost as well as diagnostic yield and reversibility.

Recommendations for Action

The Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure recently issued a set of recommendations representing compromise rather than consensus.[1] They are useful as a starting point for discussion. While the confirmation process ideally should focus on assessing persistence of elevated blood pressure, the Committee acknowledged the debate about what level of blood pressure represents abnormality. They noted that patients with diastolic levels greater than 120 mm of mercury at primary screening should have immediate follow-up, while those whose levels are 105 to 120 mm of mercury be followed up within one month. Confirmation should include a minimum of two determinations, later averaged, and treatment begun only after two or more determinations have been consistently elevated.

The Committee's recommendations briefly mentioned the value of systolic versus diastolic levels in predicting cardiovascular morbidity from hypertension. The Framingham study has prospectively confirmed earlier impressions that systolic measurements were better than diastolic blood pressure measurements in predicting cardiomegaly,[33] heart failure,[34] coronary artery disease[35] and strokes.[36] Electrocardiographic changes similarly correlate better with systolic than with diastolic levels.[21] Yet, for the sake of simplicity, the Committee elected to continue the traditional focus on diastolic blood pressure to define severity. Tarazi suggests[37] that firmly rooted clinical impressions buttress the Committee's position, noting that control of systolic blood pressure often produces intolerable side effects, especially in the elderly.

Techniques of Measurement

The Committee also recommended greater attention to techniques of blood pressure measurement. The American Heart Association has recommended that cuff width be equal to 40 percent of the arm circumference with the bladder encircling half the arm. Geddes and Whistler[38] confirmed that narrow cuffs overestimate and wide cuffs underestimate blood pressure but that the extent of error was usually less than 5 percent.

The normal cuff size for adults (12.5 by 23 cm) is usually adequate except for persons with obese arms who may require a large size (14 by 40 cm) or, rarely, even a thigh cuff (17.5 by 40 cm).

Traditional professional training has emphasized radial palpation to avoid the auscultatory gap, which is not necessarily eliminated by routine sphygmomanometric inflation to 200 mm of mercury and may extend over a range of 40 mm of mercury.[39] Other concerns include (1) choice of phase 4 (muffling) versus phase 5 (cessation) Korotkoff sounds for diastole and (2) observer bias. The Committee recommends the use of phase 5 sounds for diastole, except for unusual patients with a difference of more than 10 mm of mercury between phases 4 and 5, for whom both values should be recorded. More important, Wilcox's classic study of observer variability[16] suggests that most imprecision occurs between the earpieces of the stethoscope. Knowledge of past blood pressure values, digit preference and varying auditory acuity also contribute to inaccuracy and lack of reproducibility. The development of random-zero sphygmomanometers for research may ultimately be adopted in other clinical settings as well.[20] But even these devices will not alter the great biological and environmental variability in blood pressure levels.[40] Whatever measuring device is used, its accuracy must be assured by independent calibration against a mercury manometer standard, especially for aneroid manometers, which have a recognized tendency toward inaccuracy[41] but are readily standardized with simple methods.[42]

Establishment of Data Base

After confirming elevated blood pressure, a clinician can establish a data base for initial status against which to measure future complications of hypertension or its treatment. Several recent reviews describe the process of data base collection.[43,44]

The search for secondary forms of hypertension is closely bound to the baseline history and physical examination which all authorities agree constitute the core of the hypertensive diagnostic evaluation. Controversy emerges over the extent of laboratory and special studies as well as the indications for selective test application. Perhaps the spectrum of opinion is best shown in these quotations:

> If physicians would devote as much time to the treatment of the 95 [99.5] percent of hypertensive patients who have no remedial cause for their elevated blood pressure as they devote to looking for the 5 percent [0.5 percent] with curable causes, a reduction in cardiovascular mortality would soon become apparent.[45]

> Is the current revulsion at science now extending to technology and applied science? Is it possible that the ultrapragmatic and utilitarian approach is really thinly veiled anti-intellectualism?[46]

Melby's paradigmatic argument for extensive hypertensive evaluations[46] consists of five points: (1) The extent of patient noncompliance is so great that therapy should be adapted to each person and all curable forms identified. (2) Curable hypertensive patients are estimated to number 1.3 million in the United States. (3) Newer and improved diagnostic techniques will increase the yield of diagnostic evaluation. (4) The tests are neither inordinately expensive nor inconvenient. (5) The alternative of nonevaluation leaves patients at risk for toxicity of unnecessary medication.

In response, Finnerty[47] makes four observations: (1) Academic medical centers focus their clinical, teaching and research efforts on the rarer secondary forms, leaving the average practitioner poorly informed about the proper approach to asymptomatic, uncomplicated, essential hypertension. (2) Most types of secondary hypertension can be suspected after a careful history and physical examination and simple, inexpensive laboratory tests. (3) Only patients with accelerated hypertension, unsatisfactory response to customary treatment or intolerable side effects to all reasonable treatments (as well as selected white men younger than 40 and black men younger than 30) should receive extensive workups. (4) Modern drug therapy is generally well tolerated and reasonable in cost, requiring only one or two drugs in a stepped-care format.

Primary Versus Secondary Hypertension

Two fundamental issues are involved in considering primary versus secondary hypertension. First, what is the true ratio of primary (essential) to secondary (possibly curable) hypertension? And, second, what proportion of secondary forms that are detected and treated are actually cured?

Since Gifford's often cited paper in 1969,[48] a number of estimates of primary versus secondary hypertension have been made (Table 2). The importance of selection bias—that is, the way in which a particular patient is included in a study—has been increasingly recognized. As an authority on primary aldosteronism, Conn reports a 7.5

percent prevalence of this diagnosis in his referral clinic,[49] while 646 unselected patients from a community screening effort do not include a single case of aldosteronism.[50] Accordingly, the series from Imura,[51] Berglund[52] and Rudnick[53] presumably are more representative of the population at large and show remarkable similarities, although describing geographically disparate Japanese, Swedish and Canadian patients.

If we accept their mean as correct, essential hypertension outnumbers secondary forms 15 to 1. Even more relevant, however, is the proportion of ultimately cured cases among those patients found to have secondary hypertension.[54] The series shown in Table 2, as well as others,[55-57] confirm that only a small proportion of patients with renovascular hypertension benefit from surgical procedures. Only four of 665 patients (0.6 percent) from Rudnick and co-workers' series had potentially curable hypertension. In one patient with the Cushing syndrome, hypertension was recognized on physical examination and the patient was referred for further evaluation. Another patient had a demonstrable aortic coarctation but died during surgical operation. A third patient's renovascular hypertension was sought and identified after loss of previously good antihypertensive control; she still needed medication after a corrective operation. The fourth patient's hypertension cleared after she discontinued taking oral contraceptives. Ferguson[58] confirms the relatively high prevalence of contraceptive-induced hypertension with its ready reversibility.

Thus, the conclusions of newer series support the belief that the prevalence and reversibility of secondary hypertension have been greatly overestimated. While further research and extensive evaluations will remain critical for selected patients, only a minimal data base (for example, careful history, physical examination and analysis of urine, and serum creatinine, serum uric acid and serum potassium determinations) is probably necessary for all patients.

Cost of Evaluation

Cost issues are also increasingly inescapable. Ferguson's series,[58] based on a referred population, indicates that clinic evaluation averaged $164 per person for at least one initial and one follow-up visit. Dividing the total diagnostic charges by the number of diagnosed secondary forms of hypertension raised the average cost per secondary form to $2,083. Only 15 of 26 patients were actually cured by the clinic's efforts, ultimately raising the evaluation cost per cured secondary case to $3,611. Ferguson's estimates of $2 billion for comprehensive evaluations of all hypertensive Americans, as well as recognized limitations of medical resources, make widespread use of such evaluations impractical. Increasingly comprehensive protocols[59] will not substitute for improved and inexpensive treatment-oriented programs with low average costs[60] and high rates of blood pressure control.[61]

Patient Compliance

The final criteria of management success, then, are blood pressure control and prevention of hypertensive complications. Probably the single greatest determinant of success is patient compli-

TABLE 2.—*Prevalence of Primary and Secondary Hypertension*

	Author(s) and Type of Patients					
	Gifford[48] Referred	*Ferguson[58] Referred*	*Bech et al.[54] Referred*	*Imura[51] Unselected Men*	*Berglund et al[52] Unselected Men (Aged 47 to 54 years)*	*Rudnick et al.[53] Unselected*
Number of patients	4,392	241	482	422	689	665
Diagnoses (percent)						
Primary hypertension	89.0	90.0	79.0	93.0	94.2	94.3
Renal parenchymal disease	5.2	2.0	13.0	6.0	4.6	4.7
Renovascular hypertension	4.4	3.0	5.0	..	0.6	0.2
Operated	1.0	2.0	1.0	..	0.3	0.2
Cured	NA	NA	NA	..	0.0	0.0
Coarctation of aorta	0.6	..	..	..	0.1	0.2
Primary aldosteronism	0.5	0.4	0.4	1.0	0.1	..
Cushing syndrome	0.3	..	..	..	..	0.2
Pheochromocytoma	0.2	..	0.2	0.2	..	..
Oral contraceptive induced	..	0.4	1.5	..	..	0.2
Congenital adrenal hyperplasia	..	0.4	..	..	..	..
Primary hyperparathyroidism	..	..	..	..	0.3	..

NA=not available

ance.[3,28] Although a modest debate surrounds the terms *compliance, adherence* and *therapeutic alliance,* most authorities would accept Sackett's general definition of compliance as "the extent to which a patient's behavior (in terms of taking medications, following diets or executing other lifestyle changes) coincides with the clinical prescription."[62] One could add continuation in therapy as another component of compliance—that is, keeping appointments and maintaining a continuing relationship with a source of clinical care for therapy.

The topic of patient compliance has received growing attention, with publication of several useful, scholarly reviews on compliance in general[63-72] and hypertensive compliance in particular.[3,73,75] The literature has focused on four major areas of investigation: documentation of the prevalence of noncompliance and its consequences, search for predictors of noncompliance, assessment of alternative methods of measuring patient compliance, and design and evaluation of specific compliance-improving interventions.

Prevalence of Noncompliance

Considerable documentation now exists about the high prevalence of noncompliance. Complete failure to take medication as prescribed occurs in 25 percent to 50 percent of both chronic and acute outpatients[65] and incomplete compliance in up to 92 percent of patients with acute, ambulatory conditions.[76] In addition, 4 percent to 35 percent of patients misuse their medication in a manner that poses a serious threat to their health,[65] both in overdosage and underdosage.[77] The consequences of such widespread poor compliance range from simple failure of therapeutic response to frank drug toxicity with occasional mortality. In addition, appointment-keeping behavior,[78,79] occurrence of life-style modification,[80] and treatment continuation rates[81,82] all vary greatly and indicate that there are relatively high proportions of noncompliant patients.

Predictors of Noncompliance

To plan appropriate interventions many investigators have focused on predictors of noncompliance, gradually listing more than 200 possible factors.[83] As Sackett indicates,[84] however, the sheer number of determinants, their great potential for interaction and the many possibilities for idiosyncratic reactions make the task of controlling them almost impossible. Many of the factors, moreover, like age or psychiatric illness, cannot be readily altered. Table 3 summarizes the most important factors documented by the literature.

Perhaps most important, no pathognomonic features of noncompliers exist. While many clinicians may have prejudices that patients of a lower social class or those poorly educated are less likely to comply with treatment programs, controlled studies show conflicting positive[85,86] and negative[87-89] correlations. Not surprisingly, health

TABLE 3.—*Summary of Important Predictors of Compliance**

Associated With Improved Compliance	*Associated With Poor Compliance*	*No Consistent Association*
	Extreme old age	Other ages
	Extreme poverty	Other incomes
	Social isolation	
Perception of		
• serious disease		Objective seriousness
• personal susceptibility		Objective susceptibility
• treatment's effectiveness		Objective effectiveness
• risks of and obstacles to treatment		Objective risks and obstacles
		Patient intelligence
Knowledge of regimen		Knowledge about disease
	Psychiatric diagnoses	Other diagnoses
Consistent therapist		Therapist prediction
Patient satisfaction		
Increased supervision		
Increased regimen simplicity	Increased regimen complexity	
	Requiring major life style change	
	Treatment side effects	
	Treatment duration	
	Safety containers for medication	

*Adapted from Sackett[8]

professionals cannot accurately predict noncompliance or compliance,[90-92] given the complexity of involved factors. The complexity increases further when considering that compliance varies for each component of a regimen (such as medication, appointments and life-style changes) as well as for each subcomponent (for example, medication for symptoms or prophylactic medication).[93]

Measuring Compliance

Difficulties in measuring compliant behavior reflect inadequate sensitivity and specificity. The customary approaches of using self-reporting,[94] pill or bottle counts,[95,96] drug level measurements in physiologic fluids[97] and inert marker substances like riboflavin[98] all fail to indicate patterns of noncompliance accurately and to give clues for intervention. The whole issue has been largely ignored by drug trial clinical research,[99] although compliance bias can substantially affect measures of clinical effectiveness.[100] Few investigators have focused on practical, efficient and unobtrusive methods of compliance measurement that could be used by the average clinician,[73] although a number of promising techniques have been described in research settings.[101,102]

Compliance-Improving Interventions

While struggling with technical problems of measuring differences in compliance outcome, a growing number of investigators have attempted specific interventions to improve patient compliance. The work has underlined several crucial principles. First, logic and common sense alone are insufficient to plan successful strategies, especially when based on traditional approaches to patient care. Proposed maneuvers should be rigorously validated before receiving general acceptance.[103] As an example, Sackett and co-workers, in a randomized clinical trial of work-site and educational strategies for improving medication compliance,[104] failed to show much improvement, although it was predicted. They highlighted a second principle in a follow-up study[105] of more behaviorally oriented maneuvers: interventions successful for some persons will fail for others. Third, they noted that improved clinical outcomes required improving compliance beyond a threshold level, calculated to be 80 percent of prescribed medication for hypertension.[106] Fourth, most interventions regardless of type must be sustained to maintain a positive effect[107,108] and the early months of therapy initiation are critical for habit establishment and specific reinforcement.[82] Untested but clearly implied by the use of moderately successful, single interventions is their subsequent combination into more effective mixed interventions—perhaps a fifth principle.

These principles supply the basis for two types of management recommendations: general guidelines for optimal antihypertensive therapy and a checklist of techniques to apply to patients who fail to respond to usual management.

General Guidelines for Hypertensive Management

Optimal management of hypertension seeks to decrease blood pressure to acceptable levels (for example, no greater than 140/90 mm of mercury) without subjecting the patient to intolerable additional risks, side effects or complications of therapy. This traditional goal hides the importance of continuing therapy. Once a patient drops out of treatment, blood pressure control fails and the clinician loses future opportunities to reinforce medication and life-style change compliance. A rapid and specific method for following up all missed appointments is crucial, therefore, to minimize dropouts. Both written and telephoned reminders have been used successfully,[109] especially for patients with long intervals between visits.[110] Equally important, the treatment setting itself should be well organized, permitting specific appointments, short waiting time, personal service, a high degree of therapist continuity[111] and, perhaps when possible, using work-site locations and co-worker peer pressure.[60,61] Patient instruction should focus on specifics of the prescribed regimen, emphasizing ways to take medication within the daily routine,[112] and using both written and verbal reinforcement[113-117] and convenience packaging if available.[118,119]

The regimen itself should be as simple as possible, avoiding unnecessary additional medications and unnecessarily frequent doses. In this context, the routine addition of potassium supplements or potassium-sparing agents to diuretic regimens is undesirable because it adds to the regimen's complexity, and is physiologically unnecessary for most hypertensive patients.[120-122] Similarly, to the traditional pharmacokinetic emphasis on plasma drug levels for most antihypertensive agents has been added the recognition that biologic half-life and tissue levels correlate poorly with plasma levels. A growing literature has emerged confirming that agents like methyldopa[123] and propran-

olol[124,125] can effectively control blood pressure when given just once a day. Clinicians should strive to avoid regimens demanding more than two doses per day because the few studies examining correlations of regimen complexity and compliance suggest frequency is more critical than the number of pills.[126,127] Finally, setting an explicit goal for blood pressure helps both clinicians and patients to measure success and motivate further maneuvers when necessary, especially as part of a formal process of contract between therapists and patients.[128]

Techniques for Nonrespondents

When the explicit goals are not met, several additional techniques may help. Sackett[84] noted that, when asked nonthreateningly, a proportion of hypertensive patients acknowledged medication noncompliance and responded better to compliance-improving maneuvers than those who did not acknowledge noncompliance.[105] Simply noting that many people have difficulty taking medication and asking a patient what kinds of problems he has experienced achieves two goals. It helps to identify noncompliers who are most likely to respond to corrective interventions and it confirms a patient's impression that medication compliance is an important concern for the clinician. Without such interest, Svarstad[129] observed that compliance cannot be readily reinforced and simplistic inquiries like, "Did you have any trouble taking the pills?" are inadequate and ineffective.[129-130]

Reinforcing behavior changes such as taking medication as prescribed or making necessary modifications in life-style is essential for success. There are several types of reinforcement. A clinician can increase the frequency of visits, using each occasion to reemphasize the blood pressure goal and proper adherence to the regimen.[131] Specially trained nurses have been moderately helpful in reinforcing compliance behavior, especially for simple regimens,[132] but not in all settings.[133] Family members should attend education sessions and help remind patients of the desired behavior between visits,[134] thereby providing an added degree of supervision. Tape recording physician comments, for patients to play back after a visit, successfully reinforces the information and recommendations given. Patients or suitable family members can be taught to monitor blood pressure at home, thereby confirming the relation between medication-taking behavior and blood pressure control,[105,135] although special attention must be paid to frequent aneroid calibration[41,42] and proper blood pressure determination technique.[16] A portion of each return visit can be devoted to reviewing the results of a patient's self-reported compliance, home blood pressure determination and a previously established blood pressure goal. The clinician should praise all progress towards the desired goal, regardless of how small progress has been.

Our heightened appreciation of compliance difficulties focuses on another clinical area in which application of research findings has lagged. No simple unifactorial cause or solution exists. We are just beginning to acquire sufficient data about successful, combined interventions to assess their feasibility and cost-effectiveness.[105,136] Clarification of potential negative consequences from labeling a person as hypertensive remains important, as the trend toward increasing patient involvement continues.

Professional Adherence

No matter how impressive the results of compliance-improving interventions may be, their ultimate effect reflects acceptance by individual patients and clinicians. Just as patients are heterogeneous in their compliance, so physicians and other health professionals show great variability in clinical behavior and adherence to guidelines of optimal care. Several studies confirm pronounced physician variability in laboratory testing[137-139] and medical ordering[138] as well as overall productivity.[140,141] Although the level of quality of medical care by explicit criteria is generally only fair in academic clinics,[142,143] the correlation between process and quality of the outcome has shown inconsistent results for hypertension in particular[143] and medical care in general.[144]

Results of Professional Variability

Professional variability may have several important effects on control of hypertension. Faced with many kinds of hypertensive evaluation and treatment, a patient may conclude that none of the doctors really knows what should be done or that no really effective treatment exists. The confusion may therefore decrease motivation to comply with or continue therapy. At the same time, hypertension resembles many other disorders for which alternative modes of therapy do coexist, and most patients can achieve apparently equal outcomes with a variety of different regi-

mens. From the perspective of public policy, physician variability raises the possibility of excessive costs and unnecessary services.

Quality of Hypertensive Management

The desired level of quality of hypertensive patient care repeatedly has been found lacking. Both in patients admitted to hospital[145] and in ambulatory patients,[146-150] investigators have found consistent patterns of deficiency in detection, treatment and follow-up. Common problems include failure to carry out six functions: record blood pressure, recognize clearly abnormal blood pressure, confirm and facilitate referral for ongoing care, document details of the initial comprehensive evaluation, bring blood pressure to a specific level and maintain adequate communication to aid compliance. In an editorial accompanying one of the reports, Freis[151] points out that many physicians continue to consider essential hypertension a benign disease best treated by reassurance rather than medication. He believes that the skepticism regarding therapy is all the more surprising because few chronic diseases have more rational or better documented treatment with widely published guidelines than hypertension.[1,2] In conclusion, he calls for intensified educational efforts within the medical profession.

Physician Education

Freis leaves unspecified how to educate the medical profession. Unfortunately, traditional methods of continuing medical education appear inadequate to achieve professional behavior change. More than a decade ago, Williamson and co-workers[152] successfully changed house staff behavior by the trick of obscuring abnormal laboratory data with fluorescent tape, after conferences, formal chart audit and periodic newsletters collectively failed. Miller[153] emphasized at the same time that, while the purpose of continuing education is to improve the quality of patient care, most efforts have been misdirected. Efforts in the past decade have continued to emphasize information and content, while Miller would insist that people learn only what they want to learn. Rather than telling a physician what he needs to know, a teacher should help him want what he needs to learn. Lacking this perspective, traditional continuing education has generally not improved the quality of medical care,[154] although rare exceptions exist.[155] Simple notification of the overuse of specific laboratory tests produces negligible physician behavior change[156]—and even when change occurs, it must be continuously reinforced for lasting effect.[157] Formal medical audit activities, although highly praised by some,[158] usually fare no better in producing measurable improvement in the quality of medical care.[159] Nelson's summary of the Utah Professional Review Organization[159] suggests that educational efforts will succeed only when they are geared to individual physicians, are well supported by clinical research data, involve important aspects of care and require minimal additional effort by a physician.

Intervention for Improving Clinical Outcome

The bleak implications of such a conclusion were modified by Inui and co-workers' controlled trial of physician tutorials for management of hypertension.[160] The study involved personalized tutorials lasting for one to two hours and reviewing local experience with documented patient ignorance of hypertension and its treatment, as well as subsequent poor success in blood pressure control. Emphasizing identification and constructive interventions for noncompliant patients, the sessions stressed perceptual and attitudinal histories and examinations. Comparing similar groups of medical house staff treating similar hypertensive patients, the investigators observed that patients of tutored physicians were more knowledgeable about hypertension and its complications, more compliant with treatment regimens and had better blood pressure maintenance than patients of control physicians in the quasi-experimental format. The remarkable effectiveness of the tutorials stands in contrast to the more modest improvements reported with single interventions focused on the patient or the regimen. Physicians were thereby asked to act as patient educators and facilitators rather than diagnosticians. Finally, the study leaves little doubt that responsibility for ongoing patient noncompliance must be shared by both patient and physician, rather than by just the patient alone.

Conclusion

The issues of patient screening, disease labeling, diagnostic evaluation, patient compliance and physician adherence continue to undermine any solution to the problem of hypertension.

Screening identifies few people with sufficient, sustained disease and generally fails to provide

adequate linkage for subsequent evaluation and follow-up. By substituting case finding, with immediate follow-up of positive cases, for simple screening, many of the shortcomings are minimized and the costs of case finding better justified.

All such efforts to identify patients at risk for hypertensive complications carry potential negative consequences from the identification and labeling processes themselves. While absenteeism and scales of satisfaction and self-concept have been the only measures used, other negative consequences may be found. Urgent but well-studied efforts are needed to confirm the prevalence of labeling's negative effects and to evaluate prophylactic interventions.

Recognizing the true, lower prevalence of reversible secondary hypertension, diagnostic evaluation may justifiably concentrate on confirming cases of sustained hypertension and provide a minimal data base for most patients and extended investigations only for a selected few who are at greater risk. Economies of cost and of societal resources will result.

All efforts to identify, evaluate and treat new cases of hypertension can be sabotaged by patient noncompliance. Its high prevalence, determinant complexity, measurement difficulties and limited interventive successes make simple solutions difficult. Still, a number of specific management recommendations may be made for maximum compliance by physicians and patients.

These recommendations should bring maximal return as efforts to enhance physician adherence to established guidelines of antihypertensive management succeed. Educational efforts for physicians reflect many of the same principles as patient motivation for compliance: motivating efforts should be personal and specific, while desired behavior change should be effective and easy.

Although nontraditional, these problems of antihypertensive management are real and difficult to resolve. They deserve major attention and ultimately effective solutions, both in their own right and to protect our societal investment in antihypertensive control.

REFERENCES

1. Moser M, Buyther JR, Finnerty F, et al: Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: A cooperative study. JAMA 237:255-261, 1977

2. Julius S: Borderline hypertension: An overview. Med Clin N Am 61:495-511, 1977

3. Sackett DL: Hypertension in the real world: Public reaction, physician response, and patient compliance, *In* Genest J, Koiw E, Kuchel O (Eds): Hypertension: Physiopathology and Treatment. New York, McGraw-Hill, 1977 pp 1142-1149

4. Whitby LG: Screening for disease: Definitions and criteria. Lancet 2:819-822, 1974

5. Pierce JR, Kleinstein RN: Screening for hypertension by optometrists. Am J Public Health 67:977-979, 1977

6. Wilber JA, Barrow JG: Hypertension—A community problem. Am J Med 52:653-663, 1972

7. Harris L and Associates: The Public and High Blood Pressure: A Survey Conducted for the National Heart and Lung Association, DHEW Publ No (NIH) 74-456. Bethesda, US Dept of Heath, Education, and Welfare, 1974

8. Shapiro M, Bleho J, Curran M, et al: Problems in the control of hypertension in the community. Canad Med Assoc J 118: 137-140, 1978

9. Garbus SB, Garbus SB: Analysis of mass hypertension screening. Prev Med 5:48-59, 1976

10. Carey RM, Reid RA, Ayers CR, et al: The Charlottesville Blood-Pressure Survey: Value of repeated blood-pressure measurements. JAMA 236:847-851, 1976

11. Sokolow M, Werdegar D, Kain HK, et al: Relationship between level of blood pressure measured casually and by portable recorders and severity of complications in essential hypertension. Circulation 34:279-298, 1966

12. Alderman MH, Yano K: How prevalence of hypertension varies as diagnostic criteria change. Am J Med Sci 271:343-349, 1976

13. Roistacher RC, Liebman JS, Russell FA, et al: Decision rules for hypertension screening: Application in a poor community with endemic hypertension. Med Care 15:311-323, 1977

14. Evans JG, Rose G: Hypertension. Br Med Bull 27:37-42, 1971

15. Armitage P, Rose GA: The variability of measurements of casual blood pressure—I. A laboratory study. Clin Sci 30:325-335, 1966

16. Wilcox J: Observer factors in the measurement of blood pressure. Nursing Res 10:4-17, 1961

17. Irving JB, Kerr F, Ewing DJ, et al: Value of prolonged recording of blood pressure in assessment of hypertension. Br Heart J 36:859-866, 1974

18. Holland WW, Humerfelt S: Measurement of blood pressure: Comparison of intra-arterial and cuff values. Br Med J 2: 1241-1243, 1964

19. Wright BM, Dore CF: A random-zero sphygmomanometer. Lancet 1:337-338, 1970

20. Hunyor SN, Flynn JM, Cochineas C: Comparison of performance of various sphygmomanometers with intra-arterial blood-pressure readings. Br Med J 2:159-162, 1978

21. Ibrahim MM, Tarazi RC, Dustan HP, et al: Electrocardiogram in evaluation of resistance to antihypertensive therapy. Arch Intern Med 137:1125-1129, 1977

22. Mathieu G, Biron P, Roberge R, et al: Blood pressure determinations during medical examinations: How many? Canad J Pub Health 65:447-450, 1974

23. Labarthe DR, Hawkins CM, Remington RD: Evaluation of performance of selected devices for measuring blood pressure. Am J Cardiol 32:546-553, 1973

24. Webber LS, Voors AW, Foster TA, et al: A study of instruments in preparation for a blood pressure survey of children. Circulation 56:651-656, 1977

25. Levy RI: Wecome and overview, *In* MSD Health Information Services: High Blood Pressure Control in the Work Setting—Proceedings of the National Conference on High Blood Pressure Control. West Point, PA, Merck, Sharp, and Dohme, 1976, pp 14-16

26. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension: I. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA 202:1028-1034, 1967

27. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressures averaging 90-114 mm Hg. JAMA 213:1143-1152, 1970

28. Stason WB, Weinstein MC: Allocation of resources to manage hypertension. N Engl J Med 296:732-739, 1977

29. Haynes RB, Sackett DL, Taylor DW, et al: Increased absenteeism from work after detection and labeling of hypertensive patients. N Engl J Med 299:741-744, 1978

30. Haynes RB, Mossey JL, Sackett DL, et al: Changes in absenteeism and psychosocial function due to hypertension screening and therapy among working men. Prev Med (Abstr) 7:85, 1978

31. Gibson ES, Martin RH, Haynes RB: Mortality and morbidity in an employed population. Canad Fam Phys 22:293-302, 1976

32. Mroczek WJ: Antihypertensive therapy and reduced life-insurance premiums. Ann Intern Med 88:706-707, 1978

33. Kannel WB, Gordon T, Offutt D: Left ventricular hypertrophy by electrocardiogram: Prevalence, incidence, and mortality in the Framingham study. Ann Intern Med 71:89-105, 1969

34. Kannel WB, Castelli WP, McNamara PB, et al: Role of blood pressure in the development of congestive heart failure. N Engl J Med 287:782-787, 1972

35. Kannel WB, Gordon T, Schwartz MJ: Systolic versus diastolic blood pressure and risk of coronary heart disease: The Framingham study. Am J Cardiol 27:335-347, 1971

36. Kannel WB, Wolf PA, Verter J, et al: Epidemiologic assessment of the role of blood pressure in stroke. JAMA 214:301-306, 1970

37. Tarazi RC: Clinical import of systolic hypertension. Ann Intern Med 88:426-428, 1978

38. Geddes LA, Whistler SJ: The error in indirect blood pressure measurement with the incorrect size of cuff. Am Heart J 96: 4-8, 1978

39. Askey JM: The auscultatory gap in sphygmomanometry. Ann Intern Med 80:94-97, 1974

40. Wertheimer L: Studies in a hypertensive population. Postgrad Med J 52(Suppl 7):114-118 1976

41. Fisher HW: A nationwide sphygmomanometric calibration program. Prev Med (Abstr) 7:70, 1978

42. Grim CM, Grim CE: Self blood pressure devices are not frequently checked for accuracy. Prev Med (Abstr) 7:79 1978

43. Hickler RB: The office management of hypertension. Angiology 26 (1 Pt 1):42-53, 1975

44. Noth RH: How far to go in the diagnostic evaluation of the hypertensive adult. Primary Care 4:1-11, 1977

45. Gifford RW: Evaluation of the hypertensive patient. Chest 64:336-340, 1973

46. Melby JC: Extensive hypertensive work-up: Pro. JAMA 231:399-401, 1975

47. Finnerty FA: Extensive hypertensive work-up: Con. JAMA 231:402-403, 1975

48. Gifford RW: Evaluation of the hypertensive patient with emphasis on detecting curable causes. Milb Mem Fund Q 47: 170-186, 1969

49. Conn JW: The Evolution of Primary Aldosteronism: 1954-1967. New York, Academic Press, 1968, pp 257-291

50. Beevers DG, Nelson CS, Padfield PL, et al: The prevalence of hypertension in an unselected population, and the frequency of abnormalities of potassium, angiotensin II and aldosterone in hypertensive subjects. Acta Clin Belg 29:276-280, 1974

51. Imura O: Actual incidence of secondary hypertension. Jap Circul J 37:1040-1044, 1973

52. Berglund G, Andersson O, Wilhelmsen L: Prevalence of primary and secondary hypertension: Studies in a random population sample. Brit Med J 2:554-556, 1976

53. Rudnick KV, Sackett DL, Hirst S, et al: Hypertension in a family practice. Canad Med Assoc J 117:492-497, 1977

54. Bech K, Hilden T: The frequency of secondary hypertension. Acta Med Scand 197:65-69, 1975

55. Fairman MJ, Harpur JE, Hamilton M: Value of routine intravenous pyelography in the investigation of hypertension. Postgrad Med J 50:508-510, 1974

56. Lewis PJ, Bulpitt CJ, Sherwood T, et al: Routine intravenous urography in the investigation of hypertension. J Chron Dis 29:785-791, 1976

57. Bailey SM, Evans DW, Fleming HA: Intravenous urography in investigation of hypertension. Lancet 1:57-58, 1975

58. Ferguson RK: Cost and yield of the hypertensive evaluation: Experience of a community-based referral clinic. Ann Intern Med 82:761-765, 1975

59. Grim CE, Weinberger MH, Higgins JT, et al: Diagnosis of secondary forms of hypertension. JAMA 237:1331-1335, 1977

60. Alderman MH, Schoenbaum EE: Detection and treatment of hypertension at the work site. N Engl J Med 293:65-68, 1975

61. Alderman MH: Comparison of union-sponsored blood pressure treatment on and off the work site. Prev Med (Abstr) 7:34, 1978

62. Sackett DL: The magnitude of compliance and noncompliance, *In* Sackett DL, Haynes RB (Eds): Compliance with Therapeutic Regimens. Baltimore, Johns Hopkins University Press, 1976, pp 9-25

63. Marston MV: Compliance with medical regimens: A review of the literature. Nurs Res 19:312-323, 1970

64. Blackwell B: The drug defaulter. Clin Pharm Therap 13: 841-848, 1972

65. Stewart RB, Cluff LE: A review of medication errors and compliance in ambulant patients. Clin Pharm Therap 13:463-468, 1972

66. Blackwell B: Patient compliance. N Engl J Med 289:249-253, 1973

67. Boyd JR, Covington TR, Stanaszek WF, et al: Drug defaulting—Part 1: Determinants of compliance. Am J Hosp Pharm 31:362-367, 1974

68. Gillum RF, Barsky AJ: Diagnosis and management of patient noncompliance. JAMA 228:1563-1567, 1974

69. Smith DL: Patient compliance with medication regimens. Drug Intell Clin Pharm 10:386-393, 1976

70. Podell RN, Gary LR: Compliance: A problem in medical management. Am Fam Phys 13:74-79, 1976

71. Matthew D, Hingson R: Improving patient compliance: A guide for physicians. Med Clin N Am 61:879-889, 1977

72. Christensen DB: Drug-taking compliance: A review and synthesis. Health Serv Rep, Summer, 1978, pp 171-187

73. Podell RN, Gary LR: Hypertension and compliance: Implications for the primary physician. N Engl J Med 294:1120-1121, 1976

74. Blackwell B: Treatment adherence in hypertension. Am J Pharm 148:75-85 1976

75. Ruley EJ: Compliance in young hypertensive patients. Ped Clin N Am 25:175-182, 1978

76. Bergman AB, Werner RJ: Failure of children to receive penicillin by mouth. N Engl J Med 268:1334-1338, 1963

77. Boyd JR, Covington TR, Stanaszek WF, et al: Drug defaulting—Part II: Analysis of noncompliance patterns. Am J Hosp Pharm 31:485-491, 1974

78. Shah CP, MacBride JR, Lamb GA: Appointment systems: Why does a patient not return? Canad J Publ Health 68:148-153, 1977

79. Hertz P, Stamps PL: Appointment-keeping behavior reevaluated. Am J Public Health 67:1033-1036, 1977

80. Burnum JF: Outlook for treating patients with self-destructive habits. Ann Intern Med 81:387-393, 1974

81. Caldwell JR, Cobb S, Dowling MD, et al: The dropout problem in antihypertensive treatment: A pilot study of social and emotional factors influencing a patient's ability to follow antihypertensive treatment. J Chron Dis 22:579-592, 1970

82. Rudd P, Davidson SM, Bostwick GJ, et al: Hypertensive appointment adherence: Indicator condition and natural history. Arch Intern Med 139:545-549, 1979

83. Haynes RB: A critical review of the "determinants" of patient compliance with therapeutic regimens, *In* Sackett DL, Haynes RB (Eds): Compliance with Therapeutic Regimens. Baltimore, Johns Hopkins University Press, 1976, pp 26-39

84. Sackett DL: Patients and therapies: Getting the two together. N Engl J Med 298:278-279, 1978

85. Hurtado A, Greenlick M, Columbo T: Determinants of medical care utilization: Failure to keep appointments. Med Care 11:189-198, 1973

86. Becker MH, Kaback MM, Rosenstock IM, et al: Some influences on public participation in a genetic screening program. J Commun Health 1:3-14, 1975

87. Haefner DP, Kirscht JP: Motivational and behavioral effects of modifying health beliefs. Public Health Rep 85:478-484, 1970

88. Hecht AB: Improving medication compliance by teaching outpatients. Nurs Forum 13:112-129, 1974

89. Hulka BS, Cassel JC, Kupper LL, et al: Communication, compliance, and concordance between physicians and patients with prescribed medications. Am J Public Health 66:847-853, 1976

90. Davis MS: Variations in patients' compliance with doctors' orders: Analysis of congruence between survey responses and results of empirical investigations. J Med Educ 41:1037-1048, 1966

91. Mushlin AI, Appel FA: Diagnosing potential noncompliance. Arch Intern Med 137:318-321, 1977

92. Roth HP, Caron HS: Accuracy of doctors' estimates and patients' statements on adherence to a drug regimen. Clin Pharm Therap 21:361-370, 1978

93. Closson RG, Kikugawa CA: Noncompliance varies with drug class. Hospitals 49:89-93, 1975

94. Gordis L, Markowitz M, Lilienfeld AM: The inaccuracy in using interviews to estimate patient reliability in taking medication at home. Med Care 7:49-54, 1969

95. Roth HP, Caron HS, Hsi BP: Measuring intake of a prescribed medication: A bottle count and a tracer technique compared. Clin Pharm Therap 11:228-237, 1970

96. Rickels K, Briscoe E: Assessment of dosage deviation in outpatient drug research. J Clin Pharm 10:153-160, 1970

97. Lowenthal DT, Briggs WA, Mutterperl R, et al: Patient compliance for antihypertensive medication: The usefulness of urine assays. Curr Ther Res 19:405-409, 1976

98. Deuschle K, Jordahl C, Hobby G: Clinical usefulness of riboflavin-tagged isoniazid for self-medication in tuberculous patient. Am Rev Resp Dis 82:1-10, 1960

99. Soutter BR, Kennedy MC: Patient compliance assessment in drug trials: Usage and methods. Aust NZ J Med 4:360-364, 1974

100. Feinstein AR: "Compliance bias" and the interpretation of therapeutic trials, *In* Sackett DL, Haynes RB (Eds): Compliance with Therapeutic Regimens. Baltimore, Johns Hopkins University Press, 1976, pp 152-166

101. Moulding T, Onstad D, Sbarbaro JA: Supervision of outpatient drug therapy with the medication monitor. Ann Intern Med 73:559-564, 1970

102. Yee RD, Hahn PM, Christensen RE: Medication monitor for ophthalmology. Am J Ophthal 78:774-778, 1974

103. Sackett DL: Compliance trials and the clinician. Arch Intern Med 138:23-25, 1978

104. Sackett DL, Haynes RB, Gibson ES, et al: Randomised clinical trial of strategies for improving medication compliance in primary hypertension. Lancet 1:1205-1207, 1975

105. Haynes RB, Sackett DL, Gibson ES, et al: Improvement of medication compliance in uncontrolled hypertension. Lancet 1:1265-1268, 1976

106. Sackett DL, Haynes RB, Gibson ES, et al: The problem of compliance with antihypertensive therapy. Pract Cardiol 2:35-39, 1976

107. McKenney JM, Slining JM, Henderson HR, et al: The effect of clinical pharmacy services on patients with essential hypertension. Circulation 48:1104-1111, 1973

108. Buccicone J, McAllister RG: Failure of single-session dietary counseling to reduce salt intake in hypertensive patients. South Med J 70:1436-1438, 1977

109. Gates SJ, Colburn DK: Lowering appointment failures in a neighborhood health center. Med Care 14:263-267, 1976

110. Levy R, Claravall V: Differential effects of a phone reminder on appointment keeping for patients with long and short between-visit intervals. Med Care 15:435-438, 1977

111. Finnerty FA, Mattie EC, Finnerty FA: Hypertension in the inner city—I. Analysis of clinic dropouts. Circulation 47: 73-75, 1973

112. Zifferblatt SM: Increasing patient compliance through the applied analysis of behavior. Prev Med 4:173-182, 1975

113. Ley P, Jain VK, Skilbeck CE: A method for decreasing patients' medication errors. Psychol Med 6:599-601, 1976

114. MacDonald ET, MacDonald JB, Phoenix M: Improving drug compliance after hospital discharge. Br Med J 2:618-621, 1977

115. Gabriel M, Gagnon JP, Bryan CK: Improved patient compliance through use of a daily drug reminder chart. Am J Public Health 67:968-969, 1977

116. Wandless I, Davie JW: Can drug compliance in the elderly be improved? Br Med J 1:359-361, 1977

117. Clinite JC, Kabat HF: Improving patient compliance. J Am Pharm Assoc NS 16:74-76, 85, 1976

118. Linkewich JA, Catalano RB, Flack HL: The effect of packaging and instruction on outpatient compliance with medication regimens. Drug Intell Clin Pharm 8:10-15, 1974

119. Myers CE: Patient experiences with a child-resistant prescription container. Am J Hosp Pharm 34:255-258, 1977

120. Down PF, Polak A, Rao R, et al: Fate of potassium supplements in six outpatients receiving long-term diuretics for oedematous disease. Lancet 2:721-724, 1972

121. Kosman ME: Management of potassium problems during long-term diuretic therapy. JAMA 230:743-748, 1974

122. Wilkinson PR, Issler H, Herp R, et al: Total body and serum potassium during prolonged thiazide therapy for essential hypertension. Lancet 1:759-762, 1975

123. Wright JM, McLeod PJ, McCullough W: Antihypertensive efficacy of a single bedtime dose of methyldopa. Clin Pharm Therap 20:733-737, 1977

124. Westerlund A, Hansson L: Once-daily treatment of hypertension (Letter). Br Med J 3:877, 1976

125. Wilson M, Morgan G, Morgan T: The effect on blood pressure of beta adrenoceptor blocking drugs administered once daily and their duration of action when therapy is ceased. Br J Clin Pharm 3:857-861, 1976

126. Gatley MS: To be taken as directed. J Roy Coll Gen Prac 16:39-44, 1968

127. Porter AMW: Drug defaulting in a general practice. Br Med J 1:218-222, 1969

128. Steckel SB, Swain MA: Contracting with patients to improve compliance. Hospitals 51:81-84, 1977

129. Svarstad B: The Doctor-Patient Encounter, PhD dissertation, University of Wisconsin, 1974. Ann Arbor, University Microfilm

130. Stewart MA: Physician knowledge of and response to patients' problems. Med Care 15:578-585, 1977

131. Haynes RB, Sackett DL, Taylor DW: The practical management of low compliance with antihypertensive therapy: A guide for the busy practitioner. Elmsford, NY, Boehringer Ingelheim Ltd, 1978, pp 1-20

132. Tagliacozzo DM, Luskin DB, Lashof JC, et al: Nurse intervention and patient behavior: An experimental study. Am J Public Health 64:596-603, 1974

133. Spector R, McGrath P, Uretsky N, et al: Does intervention by a nurse improve medication compliance? Arch Intern Med 138:36-40, 1978

134. Caplan RD, Robinson EAR, French JRP, et al: Adhering to Medical Regimens: Pilot Experiments in Patient Education and Social Support. Ann Arbor, Institute for Social Research (University of Michigan), 1976, pp 1-284

135. Carnahan JE, Nugent CA: The effects of self-monitoring by patients on the control of hypertension. Am J Med Sci 269: 69-73, 1975

136. Stamler R, Gosch RC, Stamler J, et al: Adherence and blood-pressure response to hypertension treatment. Lancet 2: 1227-1230, 1975

137. Freeborn DK, Baer D, Greenlick MR, et al: Determinants of medical care utilization: Physicians' use of laboratory services. Am J Public Health 62:846-853, 1972

138. Schroeder SA, Kenders K, Cooper JK, et al: Use of laboratory tests and pharmaceuticals: Variation among physicians and effect of cost audit on subsequent use. JAMA 225:969-973, 1973

139. Lyle CB, Citron DS, Sugg WC, et al: Cost of medical care in a practice of internal medicine: A study in a group of 7 internists. Ann Intern Med 81:1-6, 1974

140. Lyle CB, Applegate WB, Citron DS, et al: Practice habits in a group of eight internists. Ann Intern Med 84:594-601, 1976

141. Reid RA, Lantz KH: Physician profiles in training the graduate internist. J Med Educ 52:301-307, 1977

142. Goetzl EJ, Cohen P, Downing EK, et al: Quality of diagnostic examinations in a university hospital outpatient clinic. Ann Intern Med 78:481-489, 1973

143. Nobrega FT, Morrow GW, Smoldt RK, et al: Quality assessment in hypertension: Analysis of process and outcome methods. N Engl J Med 296:145-148, 1977

144. Kane RL, Gardner J, Wright DD, et al: Relationship between process and outcome in ambulatory care. Med Care 15: 961-965, 1977

145. Frohlich ED, Emmott C, Hammersten JE, et al: Evaluation of the initial care of hypertensive patients. JAMA 218: 1036-1038, 1971

146. Langfeld SB: Hypertension: Deficient care of the medically served. Ann Intern Med 78:19-23, 1973

147. Brook RH, Appel FA: Quality-of-care assessment: Choosing a method for peer review. N Engl J Med 288:1323-1329, 1973

148. Mroczek WJ, Martin M, Finnerty FA: Detection of hypertension: Blood pressure determination in outpatient clinics of medical school-affiliated training programs. JAMA 231:1264-1266, 1975

149. LoGerfo JP: Hypertension: Management in a prepaid health care project. JAMA 233:245-248, 1975

150. Alderman MH, Ochs OS: Treatment of hypertension at the university medical clinic. Arch Intern Med 137:1707-1710, 1977

151. Freis ED: The mismanagement of hypertension. Arch Intern Med 137:1669, 1977

152. Williamson JW, Alexander M, Miller GE: Continuing education and patient care research. JAMA 201:938-942, 1967

153. Miller GE: Continuing education for what? J Med Educ 42:320-326, 1967

154. Lewis CE, Hassanein RS: Continuing medical education—An epidemiologic evaluation. N Engl J Med 282:254-259, 1970

155. Laxdal OE, Jennett PA, Wilson TW, et al: Improving physician performance by continuing medical education. Canad Med Assoc J 118:1051-1058, 1978

156. Eisenberg JM, Williams SV, Garner L, et al: Computer-based audit to detect and correct overutilization of laboratory tests. Med Care 15:915-920, 1977

157. Eisenberg JM: An educational program to modify laboratory use by house staff. J Med Educ 52:578-581, 1977

158. Sanazaro PJ: Medical audit, continuing medical education and quality assurance. West J Med 125:241-252, 1976

159. Nelson AR: Orphan data and the unclosed loop: A dilemma in PSRO and medical audit. N Engl J Med 295:617-619, 1976

160. Inui TS, Yourtee EL, Williamson JW: Improved outcomes in hypertension after physician tutorials: A controlled trial. Ann Intern Med 84:646-651, 1976

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Amyloidosis and Periodic Peritonitis (Familial Mediterranean Fever)

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Some reports indicate that amyloidosis is a rare occurrence in persons with periodic peritonitis (familial Mediterranean fever), while others seem to show it occurs relatively frequently. Two cases were seen among 80 patients in Iraq. Twenty-one consecutive rectal biopsies were negative for amyloidosis. The variation in reported incidence is partly real and partly apparent. Amyloidosis occurs frequently in certain ethnic groups, and it is possible that there are two traits, one for periodic peritonitis and the other for amyloidosis.

PERIODIC PERITONITIS (recurrent polyserositis, familial Mediterranean fever) is still an enigma in many respects. Several decades after the first description of a case by Janeway,[1] the cause and the pathogenesis of the episodes are still unknown. Furthermore, there are some variations in the course and the clinical features according to different investigators.[2-4] One important feature is the occurrence of amyloidosis and renal involvement.

In 1975 we reported only two cases of amyloidosis among 50 patients with periodic peritonitis.[4] No additional cases were discovered among more than 80 patients studied later. We then decided to carry out a careful search for amyloidosis in cases of periodic peritonitis.

Patients and Methods

Repeated physical examinations, analyses of urine and measurements of blood urea, serum creatinine and plasma proteins were made. In all, 25 patients with periodic peritonitis were seen during 1977. Rectal biopsy was done in 21 cases, all of which fulfilled the diagnostic criteria of periodic peritonitis.[3,4] These criteria are recurrent episodes of abdominal pain, sometimes with chest pain or arthritis accompanied by fever lasting one to three days, a course extending over several years and an absence of other diseases that could explain the clinical features.

The patients ranged in age from 15 to 51, with a mean age of 29.5 years (see Table 1). Thirteen were male and eight were female. Fourteen were Iraqui Arabs, three were Armenian, three Assyrian and one was a Kurd.* Eleven records were derived from the previously reported series and the remaining ten were new patients. The duration of illness ranged from 4 to 31 years, with a mean of 15.7 years.

Specimens of rectal mucosa excised at biopsy were stained with hematoxylin-eosin stain and Congo red and examined by polarizing microscopy. No evidence of amyloidosis was found in any of the specimens. Repeated physical exami-

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*The population at risk includes Arabs, Kurds, Turkomans, Armenians and Assyrians.

nation failed to show organomegaly or edema. At least five spot urine tests were done in each case and no proteinuria was shown. Renal function remained normal. All patients were in good health otherwise.

Discussion

The relation of amyloidosis to periodic peritonitis is of importance because it is a decisive factor in the prognosis and those who are affected ultimately succumb.[2,3,5] The diagnosis of amyloid disease is easy when preexisting disease known to induce it is present, together with edema, organomegaly, albuminuria and the serum protein changes. Definitive diagnosis is made by rectal biopsy. This simple, cheap, reliable and harmless procedure remains the histological *sheet anchor* for the diagnosis of amyloidosis.[6]

Amyloidosis in periodic peritonitis was first described by Mamou and Cattan.[7,8] According to different authors there is great variation regarding the prevalence of this fatal complication, ranging between its nonexistence[9-12] to an incidence as high as 60 percent.[2,3,13,14] According to Sohar and co-workers, few patients escape it.[2] If so, this would seriously question some names given to periodic peritonitis[19] implying its benign course.

The discrepancies among different authors' reports were analysed by Eliakim.[3] The variation is partly real and partly apparent. One of the reasons given by Sohar and co-workers for the high incidence of amyloidosis in their series was their high index of suspicion.[2] Our index of suspicion was indeed high in our first report as obvious from its title "Periodic Peritonitis—Report of 41 Cases Without Amyloidosis."[4] Since that report we have added rectal biopsy as a means of investigation.

Most cases of amyloidosis had been discovered because of persistent albuminuria or the nephrotic syndrome, or both, and less often by tissue analysis. Diagnosis of the preclinical stage of amyloidosis by renal biopsy was rarely made.[2]

Albuminuria is not an unusual phenomenon in clinical medicine. The number of its causes is formidable and to the many causes reported by Eliakim and his group,[16] certainly others could be added including *analgesic kidney*. Patients with recurrent painful illness lasting for years are apt to take different analgesic drugs. The total period of analgesic drugs intake could be of significance in periodic peritonitis because of its frequent episodes. The presence of proteinuria in periodic peritonitis is not necessarily synonymous with amyloidosis.[16] It was unfortunate that the mere presence of albuminuria in patients was considered by some authors as evidence of amyloidosis. This was one of the factors contributing to false conclusions.[3,16] In our earlier report[4] four patients

TABLE 1.—*Twenty-One Consecutive Patients Showing Age, Sex, Duration of Illness and Their Ethnic Origin*

Patient No.	*Age*	*Sex*	*Duration of Illness (years)*	*Ethnic Origin*	*Fever*	*Abdominal Pain*	*Abdominal Surgery*	*Other Serous Membrane Involvement*
1 ...	36	F	30	Arab	+	+	+	.....
2 ...	32	M	17	Armenian	+	+	−	.....
3 ...	28	M	10	Arab	+	+	P	.....
4 ...	19	M	9	Armenian	+	+	−	Synovitis
5 ...	33	F	17	Arab	+	+	+	.....
6 ...	21	M	9	Arab	+	+	P	Arthralgia without synovitis
7 ...	29	M	8	Kurd	+	+	−	.....
8 ...	20	F	16	Arab	+	+	P	.....
9 ...	15	F	11	Assyrian	+	+	−	.....
10 ...	35	M	12	Arab	+	+	+	.....
11 ...	31	M	12	Armenian	+	+	P	Arthralgia without synovitis
12 ...	22	F	22	Assyrian	+	+	P	Retrosternal pain
13 ...	51	M	31	Arab	+	+	+	.....
14 ...	43	M	31	Arab	+	+	+	.....
15 ...	27	M	4	Arab	+	+	P	.....
16 ...	30	F	25	Assyrian	+	+	+	Synovitis
17 ...	36	M	26	Arab	+	+	+	Arthralgia without synovitis
18 ...	33	M	12	Arab	+	+	P	.....
19 ...	35	F	20	Arab	+	+	+	.....
20 ...	23	M	10	Arab	+	+	+	.....
21 ...	19	F	16	Arab	+	+	+	.....

P = abdominal surgical operation was proposed by doctors but refused by patients.

had transient albuminuria but were not shown to have amyloidosis after careful and prolonged follow-up. Recently Schwabe and Peters[12] reported on 100 cases of periodic peritonitis (familial Mediterranean fever) without a single case of amyloidosis in spite of what appeared to be a high index of suspicion and in spite of carrying out biopsy studies of various tissues in high-risk cases. Two of their patients had albuminuria.

A low incidence of amyloidosis among Arabs and Armenians has been reported by many authors.[9,15,17] The only two cases of amyloidosis in our series of 80 patients were in Arabs. The apparent differences in the incidence of amyloidosis is due to the method of choosing series of cases, which is affected by the interests of the authors.

Amyloidosis affected 12 percent of a total of 1,017 patients collected from different series.[3] The percentage increased to 28 percent when six series with low incidence of amyloidosis were not included.[9,11,15-18] Some of the unauthenticated cases included in some series may have given rise to an apparent high incidence. It is also possible that pooling of chronic and difficult cases or cases of critically ill patients may give a higher figure in a medical center as compared with other locations. This could explain the variable incidence of amyloidosis reported by different authors from the same geographical area and dealing with the same ethnic group.[2,3,14,17]

As noted by some authors,[2] it seems unacceptable to include cases of phenotype II among amyloid cases, especially when the patients have died without other diagnostic features of periodic peritonitis (familial Mediterranean fever) developing. The possibility of primary amyloidosis always exists if the other factors are excluded. It was mentioned that the development of amyloidosis has no relationship to the time of onset, type, severity, or the number and frequency of episodes.[2,3] About 90 percent of the cases reported occurred in patients younger than 40, and in our two cases amyloidosis started at the ages of 11 and 19 years, respectively. Furthermore, Sohar suggested that amyloidosis could have started at birth in a child who had proteinuria at the age of 2 years.[2]

It is difficult to reconcile the lack of relationship between the duration of the disease and the development of this complication whatever may be the pathogenesis, assuming that amyloidosis is either a complication or part of the disease process. On the other hand, some of our patients had periodic peritonitis for more than 30 years without amyloidosis developing. The high incidence of amyloidosis among Sephardic Jews where the family history is also strong, may be related to the fact that they also have a much higher consanguinity rate than unaffected people.

As we suggested previously, there may be two variants of periodic peritonitis, one of which is characterized by high association of amyloidosis, high family history and strong consanguinity. Thus, it is not certain that patients who have the same or similar clinical features described under different names[2,4,15] belong to a single genotype. It is conceivable that there are two genetic traits, one for periodic peritonitis and the other for amyloidosis. Both of these traits may be present in the same ethnic group, becoming apparent after intermarriage. Or some ethnic groups like the Sephardic Jews and the Turks may be more predisposed for renal involvement.

REFERENCES

1. Janeway TC, Mosenthal H: An unusual paroxysmal syndrome probably allied to recurrent vomiting with a study of the nitrogen metabolism. Trans Assoc Am Physician 23:504-518, 1908

2. Sohar E, Gafni J, Pras M, et al: Familial Mediterranean fever—A survey of 470 cases and review of literature. Am J Med 43:227-253, 1967

3. Eliakim M: Incidence of amyloidosis in recurrent polyserositis (familial Mediterranean fever). Isr J Med Sci 6:2-8, Jan-Feb, 1970

4. Bakir F, Murtadha M: Periodic peritonitis, report of 41 cases without amyloidosis. Trans Royal Soc Trop Med & Hygiene 69:111-117, 1975

5. Heller H, Sohar E, Gafni J, et al: Amyloidosis in familial Mediterranean fever. Arch Intern Med 107:539-550, 1961

6. Tribe CR: Diagnosis of amyloidosis. Br Med J 2:943, 1976

7. Mamou H, Cattan R: La maladie periodique (sur 14 cas personnels dont 8 compliqués de nephropathies). Sem Hop Paris 28:1062-1070, 1952

8. Mamou H: Maladie Periodique Amylogene. Sem Hop Paris 31:388, 1955

9. Reinmann HA, Moadie J, Semerdjian S, et al: Periodic peritonitis—Heredity and pathology—Report of 72 cases. JAMA 154:1254-1259, 1954

10. Shapiro TR, Ehrenfeld EN: Recurrent polyserositis (periodic disease, familial Mediterranean fever) in children. Pediatrics 30: 443-449, 1962

11. Oganesyan LA, Farmaniyan AK, Avetisyan BA: On the problem of the so-called periodic disease. Klin Med (Mosk) 43: 19-23, 1965

12. Schwabe AD, Peters RS: Familial Mediterranean fever in Armenians—Analysis of 100 cases. Medicine (Baltimore) 53: 453-462, 1974

13. Vinogradova OM: K. voprosv o porazhenii Pochek Pri Periodochesskoi Bolezni. Ter Arkh 39:73-76, 1967

14. Ozer FL, Kaplaman E, Zileli S: Familial Mediterranean fever in Turkey—A report of twenty cases. Am J Med 50:336-339, Mar 1971

15. Siegal S: Familial paroxysmal polyserositis—Analysis of 50 cases. Am J Med 36:893-918, 1964

16. Eliakim M, Rashmilewitz M, Rosenmann E, et al: Renal manifestations in recurrent polyserositis (familial Mediterranean fever). Isr J Med Sci 6:228-245, Mar-Apr 1970

17. Ehrenfeld EN, Eliakim M, Rachmilewitz M: Recurrent polyserositis (familial Mediterranean fever, periodic disease)—A report of 55 cases. Am J Med 31:107-123, 1961

18. Grashtchenkov NI, Wein AM, Solovieva AD, et al: The syndrome of the so-called periodic diseases and hypothalamic disorder, *In* Periodic and Paroxysmal Disorders in the Neurological Clinic. Moscow, Neuropathological and Psychiatric Society, 1963

19. Seigal S: Benign paroxysmal peritonitis. Ann Intern Med 23:1-21, 1945

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Candida Pneumonia

Experience With 20 Patients

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Case reports of 20 patients with histologic evidence of Candida pneumonia at autopsy were studied retrospectively. Most of the patients had had malignant conditions or immunosuppressive disorders, or had been treated by immunosuppressive agents such as steroids. Clinical findings included cough, purulent sputum and invariable hypoxia. Of the 20 patients, 14 had positive sputum cultures, 6 had positive blood cultures and 6 had positive urine cultures for Candida organisms. Findings on chest radiographs of most of the patients showed diffuse bronchopneumonia with confluent areas of air space consolidation. Five patients had been suspected of having Candida pneumonia and were treated empirically with amphotericin B, but none survived.

PRIMARY CANDIDA PNEUMONIA is rare, occurring most often in patients receiving immunosuppressive or broad-spectrum antibiotic therapy for a variety of diseases.[1,2] The diagnosis of Candida pneumonia is difficult to establish because isolation of the yeast in cultures correlates poorly or not at all with histologic evidence of lung infection.[3]

We have reviewed the clinical, radiographic and laboratory findings in 20 patients in whom pathologic evidence of Candida pneumonia was found at autopsy, thereby limiting the confirmation of the diagnosis to culture findings only.

Methods

We undertook a retrospective study of all cases of pulmonary candidiasis diagnosed at autopsy from 1974 through 1978. Patients were included in the study only if there was histologic evidence of invasive candidiasis as shown by yeast and pseudohyphae invading viable lung tissue. Patients who had positive lung tissue cultures at autopsy but no histologic evidence of parenchymal involvement were excluded.[4] We reviewed the clinical charts, radiographs of the chest and autopsy reports for all patients. Among the 20 patients selected for the study, 8 were female and 12 were male, ranging in age from 1 month to 64 years. Candida organisms were identified in histologic specimens after staining with both hematoxylin-eosin and periodic acid-Schiff. Only round or oval yeast forms in clusters and pseudohyphae that were connected to neighboring blastospores were considered Candida. Special culture studies were done by the method of Silva-Hutner.[5-7]

We were not able to determine the source of infection in cases in which there was multiorgan involvement. In patients in whom esophageal candidiasis was diagnosed, pneumonia was as-

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TABLE 1.—*Underlying Diseases, Radiographic Findings, Results of Cultures, Associated Organisms and Premortem Diagnoses in 20 Patients With Evidence of Candida Pneumonia*

Case No.	*Underlying Disease(s)*	*Chest Radiograph*	*Other Organ Involvement Confirmed at Autopsy*	*Sputum Culture*	*Blood Culture*	*Urine Culture*	*Lung Tissue Culture*	*Post-mortem Blood Culture*	*Associated Organism(s) Obtained from Lung Tissue*	*No. of Days of Treatment With Amphotericin B (0.5 to 1 mg per kg of body weight)*
1	AML*	Bilateral pneumonia	Multiple organs	+	+	−	+	+	0	5
2	ALL*	Patchy infiltrates	Multiple organs	+	+	+	+	+	0	0
3	AML*	Diffuse infiltrates	Multiple organs	+	+	+	+	+	0	6
4	Colon carcinoma*	Bilateral pneumonia	−	−	−	−	+	+	0	0
5	Lymphoma and colon carcinoma*	R middle lobe pneumonia	Esophagus	+	−	−	+	−	0	0
6	Multicentric glioma*	R middle and lower lobe pneumonia; and R pleural effusion	−	+	−	−	+	−	0	0
7	Malignant histiocytosis*	Diffuse pulmonary infiltrates and L pleural effusion	−	+	−	−	+	−	Staphylococcus	0
8	Waldenström disease*	Diffuse bronchopneumonia	Multiple organs	+	−	−	+	−	Pseudomonas	0
9	Bone marrow transplant*	R upper lobe infiltrates	−	−	−	−	+	+	0	0
10	SLE†	Bilateral pneumonia and L pleural effusion	−	+	+	−	+	+	0	0
11	Fulminant† hepatic failure	Diffuse infiltrates	Multiple organs	+	+	+	+	+	0	0
12	Gaucher disease*	R middle lobe pneumonia and L pleural effusion	−	−	−	−	+	−	0	0
13	Renal failure and jejunoileal bypass	Diffuse bronchopneumonia	Multiple organs	+	−	+	+	+	Nocardia and Staphlococcus	5
14	Intracerebral hemorrhage†	Diffuse bronchopneumonia	−	−	−	−	+	−	0	0
15	Werdnig-Hoffmann disease	Bilateral pneumonia	Esophagus	+	−	−	+	−	Pseudomonas and Klebsiella	0
16	Polyarteritis and renal failure†	Bilateral pneumonia and L pleural effusion	−	+	−	−	+	−	Pseudomonas and Aspergillus	0
17	Cranial surgery†	Bilateral pneumonia	−	−	−	−	+	−	Pseudomonas	0
18	Pemphigus vulgaris†	Diffuse bronchopneumonia	−	+	−	+	+	−	0	4
19	Tetralogy of Fallot pulmonary atresia	Diffuse bronchopneumonia	Multiple organs	+	+	+	+	+	0	6
20	Prematurity	Diffuse bronchopneumonia	−	−	−	−	+	−	0	0

+ = positive − = negative AML = acute myeloblastic leukemia ALL = acute lymphoblastic leukemia L = left R = right SLE = systemic lupus erythematosus

*On chemotherapy.
†On steroids.

sumed to be due to direct extension into the tracheobronchial tree, and from there into the pulmonary parenchyma. However, hematogenous spread cannot be ruled out in these cases.

Results

Table 1 lists the underlying diseases, radiographic findings, results of cultures, associated organisms found in lung tissue specimens and premortem diagnoses in the 20 cases studied. All patients had serious underlying diseases requiring cytotoxic, immunosuppressive or antibiotic therapy or a combination of three therapies. Seven patients had multisystem infections involving the lungs and three or more other organs. Two other patients with esophageal candidiasis had pulmonary involvement. In the remaining 11 patients, Candida infection was identified only in the lungs.

Clinical Findings

Clinical presentations were characterized by cough, expectoration of purulent material (all patients), occasional hemoptysis (four patients) and invariable hypoxemia (all patients). There was neither evidence of candidal ophthalmitis nor valvular heart disease among these patients. No clinical finding specifically suggested Candida pneumonia as reported by others.[8] Of the 20 patients, 14 had low leukocyte counts (range 800 to 3,000 per cu mm).

None of the patients were admitted to hospital for Candida infection. All were admitted because of their underlying diseases. Findings on x-ray studies of the chest were normal, and Candida pneumonia occurred while the patients were in hospital. The average hospital stay was 17 days (range 2 to 60 days). There was no correlation between the onset of pneumonia and the number of days in hospital. Four patients had positive cultures for Pseudomonas and two for Staphylococcus during their hospital course. However, in these patients there were no abnormal pulmonary findings at the time these cultures were done.

Radiographic Findings

Of the patients, 16 had diffuse bronchopneumonia with widespread involvement of the lungs and confluent areas of air space consolidation (Figure 1) that could not be differentiated from the adult respiratory distress syndrome, pulmonary edema or other types of bronchopneumonia.[9] Four patients had localized pneumonia, which was confined to the right middle lobe in three.

Figure 1.—Radiograph of the chest shows confluent areas of air space consolidation with diffuse air bronchograms.

Five patients had pleural effusions, an uncommon finding in Candida pneumonia.[10] Each of these five patients had congestive heart failure at some point during their hospital stay; this could have been a factor in the development of pleural effusions because histologic evidence of pleural invasion was found in only one case.

Cultures for fungi of sputum, blood and urine were obtained for all patients. Candida was cultured in the sputum of 14 patients, in the antemortem blood specimens of six and in urine samples of six. All of the blood and urine cultures were positive within four days after development of clinical symptoms and abnormal findings on x-ray studies of the chest. Nine patients had positive blood cultures at autopsy. Cultures of lung tissue specimens at autopsy were positive for Candida in all 20 patients and in six patients lung specimens yielded other organisms as well. Lung biopsy specimens had not been obtained from any of the patients before death because of the severity of their clinical conditions. In two patients bronchoscopy (brushings and washings) was done but did not establish the diagnosis. Serologic tests for diagnosis were not carried out in any of these patients.

Pathologic Features

The lung parenchyma of all patients was by definition invaded by pseudohyphae and yeast

forms. There were variable numbers of microabscesses, granulomata and areas infiltrated by polymorphonuclear leukocytes and histocytes. Mild to moderate pulmonary hemorrhaging was observed in most cases. In 16 patients there was pathological evidence of Candida pneumonia in two separate lobes or more, and in four there was evidence of Candida pneumonia in only one lobe.

Discussion

Candida pneumonia was first described in 1771 by Rosen Von Rosenstein;[7] later Castellani reported Candida pneumonia in tea tasters in Ceylon.[11] Since then, there have been only scattered reports of the disease.

The most common predisposing factor reported has been immunosuppression—mostly of malignant diseases.[12-14] As expected, therefore, 16 patients in our series had primary malignant conditions or immunosuppressive disorders, or both. Prolonged, broad-spectrum antibiotic therapy and corticosteroid therapy are also common predisposing factors.[2,15] Consistent with this observation, all our patients were receiving broad-spectrum antibiotics, and 16 had received steroids or immunosuppressive agents as well at some time during their hospital course.

Because there is little correlation between findings on culture of lung specimens obtained at autopsy and histologic evidence of invasive pulmonary candidiasis, many published reports of Candida pneumonia may not actually represent this disease.[4] Therefore, it appears likely that at present, a diagnosis can be established only by taking lung biopsy specimens at autopsy. Postmortem lung cultures were positive in all of our cases that had histologic evidence of invasion, but were also positive in a large number of patients who had no morphologic evidence of this disease as expected. Sputum cultures are not helpful in establishing a diagnosis of Candida pneumonia because we have found that the incidence of Candida in sputum is common in patients with no histologic evidence of pulmonary invasion with this fungus; this also has been reported by others.[3] Quantitative sputum cultures may be helpful in such cases to avoid false-positive diagnoses.[16] Frequently, several organisms including Candida are found in the lung. In our series, cultures of six lung specimens obtained at autopsy grew various other organisms.

Fiberoptic bronchoscopy has been of little value in diagnosing Candida pneumonia because it is impossible to avoid oropharyngeal contamination of the bronchoscope with this fungus.[16] Available tests for anticandidal antibodies are of no help because of their low sensitivity and specificity.[18] Taking an open lung biopsy specimen is the most rational procedure for diagnosing Candida pneumonia.[10] Recognizing Candida in sections stained by conventional methods is relatively easy and is, therefore, the best technique for confirming a diagnosis.

All of Candida organisms in our series were Candida albicans, although several other species have been reported to cause Candida pneumonia.[19,20]

Candida endophthalmitis has been reported to have a high correlation with multiple organ involvement.[21] However, none of the patients in this series had the cottonball-like lesions of Candida ophthalmitis.

Positive blood cultures are a valuable clue in diagnosing disseminated candidiasis;[15] in our series, six of seven cases with systemic candidiasis had positive premortem blood cultures.

Candida pneumonia is generally treated with amphotericin B and 5-fluorocytosine as well. Five patients in our series received empirical amphotericin B therapy (0.5 to 1 mg per kg of body weight) during their last days in hospital; sensitivity tests were not done on these patients and they were not able to take drugs orally. All five died of cardiorespiratory arrest and hypotension, so the effectiveness of amphotericin B therapy in candida pneumonia is not known in our series.

In most of our patients death was caused by hypotension and cardiorespiratory arrest. Hypoxemia due to extensive Candida pneumonia (16 patients) may have been the cause of the arrests. Five patients had coagulopathy before death, but the possible relationship of this disorder to death is not clear.

Conclusions

(1) Candida pneumonia should be considered in patients who are receiving immunosuppressive agents and who present with pulmonary infiltrates. (2) Positive sputum culture for Candida, although not diagnostic, should alert a clinician to the possibility of Candida pneumonia, and blood and urine cultures for Candida should be obtained in such patients. (3) If cultures are positive and newly developed chest infiltrates are present, a transbronchial or open lung biopsy

should be done to determine whether tissue invasion has occurred. If it is not possible to obtain tissue specimens, empirical amphotericin B therapy may be considered. (4) All efforts to correct reversible immunosuppressive factors in patients with established pulmonary candidiasis are justified. (5) The description of clinical data in this series has been skewed by the selection process and precludes the possibility of successful therapy. Delay in diagnosis may have been a factor in delay of therapy and in the progression of the disease to death.

REFERENCES

1. Taschdjian CL, Kozinn PJ, Toni EF: Opportunistic yeast infections with special reference to candidiasis. Ann NY Acad Sci 174:606-622, 1963
2. Pillay VKG, Wilson DM, Ing TS et al: Fungus infection in steroid-treated systemic lupus erythematosus. JAMA 205:261-265, 1968
3. Baum GL: The significance of Candida albicans in human sputum. N Engl J Med 263:70-73, 1960
4. Haley LD, McCabe A: A mycological study of 71 autopsies. Am J Clin Pathol 20:35-38, 1950
5. Silva-Hutner M, Cooper BH: Medically important yeasts, *In* Lennette EH, Spaulding EH, Truant JP (Eds): Manual of Clinical Microbiology, 2nd Ed. Washington, American Society for Microbiology, 1974
6. Holman CW, Muschenheim C: Bronchopulmonary Diseases and Disorders. Hagerstown, Harper & Row, Inc, 1972
7. Winner HI, Hurley R: Candida albicans. Boston, Little, Brown & Co, 1964
8. Bode FR, Pare JAP, Fraser RG: Pulmonary diseases in the compromised host. Medicine (Baltimore) 53:255-293, 1974
9. Fraser RG, Pare PAJ: Diagnosis of Diseases of the Chest. Philadelphia, WB Saunders, Inc 1970
10. Masur H, Rosen PP, Armstrong D: Pulmonary disease caused by Candida species. Am J Med 63:914-924, 1977
11. Castellani A: Notes on certain bronchomycoses which may stimulate pulmonary tuberculosis. Am Rev Tuberc 16:541-574, 1927
12. Mills SA, Seigler HF, Wolfe WG: The incidence and management of pulmonary mycosis in renal allograft patients. Ann Surg 182:617-626, 1975
13. Rifkind D, Marchioro TL, Schneck SA, et al: Systemic fungal infections complicating renal transplantation and immunosuppressive therapy. Am J Med 43:28-38, 1967
14. Bodey GP: Fungal infections complicating acute leukemia. J Chronic Dis 19:667-678, 1966
15. Louria DB, Stiff DP, Bennett B: Disseminated moniliasis in the adult. Medicine (Baltimore) 41:307-337, 1962
16. Wilson MJB, Martin DE: Quantitative sputum culture as a means of excluding false positive reports in the routine microbiology laboratory. J Clin Pathol 25:697-700, 1972
17. Anderson HA, Fontana RS: Transbronchoscopic lung biopsy for diffuse pulmonary diseases—Technique and results in 450 cases. Chest 62:126-128, 1972
18. Filice G, Armstrong D, Yu B: Candida immunodiffusion and agglutination tests in patients with neoplastic disease—Inconsistent correlation with invasive infections. J Infect Dis 135:349-357, 1977
19. Goldstein E, Hoeprich PD: Problems in the diagnosis and treatment of systemic candidiasis. J Infect Dis 125:190-193, 1972
20. Goldstein G, Grieco MH, Fenkel G, et al: Studies on the pathogenesis of experimental Candida parapsillosis and Candida guilliermondii infections in mice. J Infect Dis 115:293-302, 1965
21. Edwards JE Jr, Foos RY, Montgomerie JZ, et al: Ocular manifestations of Candida septicemia: Review of seventy-six cases of hematogenous Candida endophthalmitis. Medicine (Baltimore) 53:47-75, 1974

Salicylates and Reversible Hearing Loss

By far the most widely used of the ototoxic agents are the salicylates, and more specifically, aspirin. . . . The ototoxicity is usually heralded by the onset of tinnitus. However, there are other compounds, that should at least be mentioned in passing, that are of this family and can also cause hearing loss. One thinks of the methyl or the sodium salicylate used in dermatologic practice as an example. The two primary characteristics of salicylate hearing loss seem to be its symmetry and its high likelihood of reversibility. It is the latter quality—this reversibilty—that allows for the common clinical practice in treating rheumatoid arthritis, wherein the aspirin dose is actually increased until the onset of tinnitus and subjective hearing loss, and then the dose is decreased until these symptoms disappear.

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Prenatal Diagnosis by Amniocentesis in 800 Pregnancies

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Prenatal diagnoses by amniocentesis have been made in 800 pregnancies at the Genetics Division of the Los Angeles County-University of Southern California Medical Center. This experience has indicated that the amniocentesis procedure is safe and highly accurate. Amniocentesis was not associated with significant morbidity or mortality for either infant or mother. The observed complications are assumed to be related to the high-risk nature of these pregnancies, the patients having been selected primarily on the basis of advanced maternal age or a previous abnormal child. The needle puncture marks, which occurred in 2.4 percent of the live births, resulted in no serious developmental or cosmetic effects to the infants. No errors in cytogenetic diagnosis are known to have occurred in this series.

BETWEEN 1969 AND 1978 the Genetics Division of the Los Angeles County-University of Southern California (LAC-USC) Medical Center completed laboratory analyses of specimens of 800 amniocenteses done for prenatal diagnosis. The total number of women referred for amniocentesis was 1,099.

Referrals

Most referrals were made to check for possible fetal chromosomal abnormality. The reasons given most frequently for referral were the following: advanced maternal age of 35 years or more (65.9 percent), a previous child with a chromosomal abnormality, usually the Down syndrome (16.2 percent) and a family history of the Down syndrome or other chromosomal abnormality (3.4 percent) (Table 1). Of the referrals, 11 (1 percent) were for a parental carrier of a chromosomal translocation or inversion as identified by a previous birth of an affected child, a family chromosomal study in three instances and a history of four abortions in another instance. Two of these families were reported previously.[1,2] In 5.5 percent of the referrals, the parents were anxious because of a family history of nonspecific mental retardation or congenital defects.

A substantial number of women were referred because of an increased risk for a fetus with a neural tube defect. Of the referrals, 6.3 percent were for the detection of a fetal neural defect because of a previously affected child, an affected parent or other family history. A smaller number of referrals was for detectable metabolic disorders and determining the sex of the fetus for X-linked disorders.

Of the 1,099 women referred for prenatal diag-

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ABBREVIATIONS USED IN TEXT

AFP = alpha-fetoprotein
LAC-USC Medical Center = Los Angeles County-University of Southern California Medical Center

nosis, 299 (27.2 percent) either decided not to have or did not have amniocentesis (Table 2). The most common reasons for not having amniocentesis were as follows: (1) concern about the safety of the procedure, (2) alleviation of parental anxiety by counseling and, in some instances, by information obtained through ultrasonographic testing, (3) a spontaneous abortion before the procedure, (4) election of a medical abortion without amniocentesis, (5) an erroneous diagnosis of pregnancy, (6) pregnancy too far advanced for amniocentesis and (7) a decision not to find out whether the fetus was abnormal. In 36 instances there was no indication for amniocentesis. Over the years, there has been a decrease in the proportion of patients who have decided not to have amniocentesis from 30 percent for the years before 1975 to 22 percent for 1978. A small proportion of older women in our population may not accept amniocentesis, possibly for cultural or religious reasons.

More than half of the referrals were from private physicians (59.8 percent), indicating that prenatal diagnosis is used primarily by women in the private sector. The self-referred patients (13.4 percent), were usually those who had had previous genetic counseling or prenatal diagnosis at the LAC-USC Genetics Division. Other referral sources were the Los Angeles County Health Department (9.4 percent), LAC-USC Medical Center (8.8 percent) and other hospitals (7.8 percent). A small number were from Regional Centers for the Developmentally Disabled (0.7 percent) and the National Foundation—March of Dimes (0.1 percent).

Laboratory Procedures

Fetal karyotyping using special banding patterns as needed, was done when the fetus was at increased risk for chromosomal abnormalities. Karyotyping was also done for fetal sex determination for nondetectable X-linked disorders. In addition

TABLE 1.—*1,099 Referrals for Amniocentesis by Indication*

Indication	*Amniocentesis* Done	*Amniocentesis* Not Done	*Subtotal (Percent)*	*Total (Percent)*
Chromosomal				1,011 (92.0)
Older maternal age			724 (65.9)	
Maternal age less than 35 years*	25	9		
Maternal age 35 to 39 years	361	112		
Maternal age more than 39 years	167	50		
Previous child with chromosomal abnormality			178 (16.2)	
Maternal age less than 35 years	111	30		
Maternal age 35 to 39 years	23	4		
Maternal age more than 39 years	8	2		
Parental carrier of chromosomal abnormality			11 (1.0)	
Maternal age less than 35 years	8	2		
Maternal age 35 to 39 years	1	..		
Maternal age more than 39 years	..	..		
Family history of chromosomal abnormality†	15	23	38 (3.4)	
Other (anxiety)†	21	39	60 (5.5)	
X-linked disease†	4	5		9 (0.8)
Inborn metabolic error†	9	1		10 (0.9)
Neural tube defect				69 (6.3)
Previous affected child			62 (5.6)	
Maternal age less than 35 years	43	15		
Maternal age 35 to 39 years	2	2		
Maternal age more than 39 years	..	..		
Affected parent†	2	1	3 (0.3)	
Family history†	..	4	4 (0.4)	
TOTAL	800	299		1,099 (100.0)

*Including maternal age 35 years at expected date of delivery.
†Maternal age less than 35 years.

to the chromosome analysis, ultrasonographic studies and alpha-fetoprotein (AFP) determinations from amniotic fluid were made in most instances.

Ultrasonography is carried out for two reasons: to identify the position of the placenta so that the safest site may be located for the amniocentesis tap, and to identify twins or gross fetal anomalies. AFP determinations are made to measure increased AFP levels, which may provide information about the presence of a fetal neural tube defect. Ultrasonographic testing and AFP measurement are now done routinely at the LAC-USC Medical Center in all instances of diagnostic amniocentesis in midpregnancy.

When the indication was increased risk for fetal metabolic disease, enzyme analysis of cultured amniotic fluid cells was used to identify the specific metabolic disease. When the indication was increased risk for fetal neural tube defect, an ultrasonographic study was carried out and AFP determined. Regardless of the specific indication, chromosome analysis was always done from cultures of amniotic fluid cells.

TABLE 2.—*Reasons for Not Doing Amniocentesis in 299 Referrals*

	Number
Procedure Indicated But Not Done	
Did not want risk of abortion or fetal injury	69
Believed risk of having abnormal child not great	31
Had spontaneous abortion before procedure	23
Opposed to medical abortion if abnormal fetus found	14
Elected medical abortion without amniocentesis	12
Decided to have ultrasound test only	9
Referred elsewhere	8
Frightened of procedure	8
Found not to be pregnant	7
Had medical complications during the pregnancy	7
Was too advanced in pregnancy	6
Wanted information not provided by procedure	6
Was tapped but no fluid obtained	6
Had twin pregnancy (anatomically difficult)	1
Decided against (inconvenient)	2
Decided against (reason unknown)	54
Procedure Not Indicated	36
TOTAL (27.2 percent of referrals)	299

Results

Results from amniocentesis are found in Table 3. Of the 800 amniocenteses, 16 (2 percent) showed abnormal chromosomal constitutions. Of these, 4 were balanced structural rearrangements and 12 were unbalanced with confirmed abnormal phenotypes, and one fetus that showed trisomy 21 was aborted spontaneously and not examined.

The National Institutes of Health (NIH) Collaborative Study reported 2 percent aneuploid fetuses by maternal age category equal to or greater than 35 years.[3] In mothers 35 years or older, the Down syndrome (trisomy 21) occurred in one (0.6 percent) of the fetuses. In the experience of the LAC-USC Genetics Division, of the 587 mothers 35 years of age or older, aneuploidy occurred in nine (1.5 percent) and the Down syndrome (trisomy 21) occurred in five (0.9 percent) of the fetuses.

Of the 412 women 35 to 39 years of age studied by amniocentesis at the LAC-USC Genetics Division, three (0.7 percent) were found to have fetuses with trisomy 21. Of the 167 women 40 to 44 years of age, one (0.6 percent) had a fetus with trisomy 21. Carter and Evans[4] found that 0.4 percent of the women 35 to 39 years old, 1.0 percent of the women 40 to 44 years old and 2.0 percent of the women 45 to 49 years old had infants with the Down syndrome.

Of the four fetuses in whom the sex was determined because of a possible X-linked disorder, all were found to be male. Two were at risk for Duchenne muscular dystrophy and were aborted, one medically and the other spontaneously. The muscle tissue from both of these males was examined by electron microscopy and found to have changes consistent with the disorder. The other

TABLE 3.—*Fetal Abnormalities Found in 800 Pregnancies*

Indication	*Fetal Abnormality*					*Number*
Chromosomal	*Aneuploidy*					
	+21	+18	+18,XXY	+13	XXX	
Maternal age						
35 to 39 years	3	..	1	1	..	5
40 to 44 years	1	1	..	..	1	3
More than 44 years	1	..	..	..	..	1
Parental carrier of inversion or translocation	Abnormal (unbalanced)					3
	Carrier (balanced)					4
Inborn metabolic error	Pompe disease					2
X-linked disorder (for fetal sex determination)	Male sex					4

TABLE 4.—*Outcomes of 800 Pregnancies with Second Trimester Amniocentesis*

	Number	*Percent*
Single infant of normal weight*	620	77.5
Set of twins†	9	1.1
Single infant of low birth weight (2,500 grams or less)‡	65	8.1
Fetal death before 28 weeks§	15	1.9
Medical abortion (for abnormal fetus)	14	1.8
Medical abortion (other)	5	0.6
Fetal death after 28 weeks	7	0.9
Pending delivery	36	4.5
Lost to follow-up	29	3.6
TOTAL	800	100.0

*1 neonatal death.
†12 of 18 infants were of low birth weight; 2 neonatal deaths.
‡7 neonatal deaths.
§12 fetal deaths occurred within one month of the procedure.

two male fetuses were at risk for X-linked hydrocephaly. One fetus was medically aborted and appeared normal. The other was carried to term, and was born with hydrocephaly.

The outcomes of pregnancy in the 800 women who had amniocentesis are presented in Table 4. No discrepancies occurred between the laboratory diagnosis of the chromosomal sex and the phenotypic sex. All fetuses diagnosed as chromosomally unbalanced or biochemically abnormal were aborted electively with two exceptions: a fetus with triplo-X that the parents decided not to abort and a fetus with trisomy 21 that was spontaneously aborted at home and not examined. Other prenatal chromosomal abnormalities were confirmed by observation of phenotype and repeat chromosome analysis after abortion. However, specimens from one fetus with clinical evidence of the Down syndrome and one fetus that showed the trisomy 18 syndrome were not successfully cultured a second time due to failure of growth from abortus tissue.

Of the 22 fetal deaths during the pregnancies, 12 occurred within one month after amniocentesis, representing a 1.6 percent fetal loss in the 752 women at risk. (Women who had medical abortions or who were lost to follow-up were not included in these calculations.) An additional three women aborted spontaneously after one month but before 28 weeks of pregnancy. The fetal deaths that occurred after amniocentesis represent a 2 percent rate of fetal loss. In addition, there were 23 women who were scheduled for amniocentesis but who aborted before the procedure. The total fetal loss rate before and after amniocentesis, therefore, was 3.6 percent. Both of these rates (2.0 percent and 3.6 percent) are less than the rate reported by Stein and associates[5] for women at comparable stages in pregnancy. Amniocentesis does not appear to increase the risk of spontaneous abortion.

Five sets of parents decided on medical abortion even though amniocentesis gave normal results. The indications for amniocentesis in these cases were advanced maternal age in four and a previous child with a neural tube defect in the fifth. Three of the fetuses were aborted because of their sex, and two were aborted for psychosocial reasons (out-of-wedlock pregnancies).

So far, 703 infants have been born alive. Of these, 77 (11.0 percent) were of low birth weight (2,500 grams or less). There were ten neonatal deaths, nine of which were related to low birth weight (Table 4). One of these low-birth-weight infants also had bilateral polycystic renal disease. The tenth neonatal death occurred in a term infant due to meconium aspiration pneumonia. Needle puncture marks were found in 17 infants, 2.4 percent of all live births. These marks were not significant in terms of fetal development or cosmetic importance.[6] Other congenital abnormalities, usually minor, occurred in 35 infants. None of these abnormalities had any apparent relationship to the procedure of amniocentesis.

Follow-up of Infants

In children born to women who had amniocentesis, follow-up studies are being done routinely for three or more years to assess physical and developmental status. These studies include a physical examination and a developmental assessment by the Gesell testing technique when the infant is 9 months old, and a complete physical and psychometric evaluation at 3 years. No serious physical or developmental problems have been found in any of the 427 children in whom studies have been done.

REFERENCES

1. Ebbin AJ, Wilson MG, Towner JW, et al: Prenatal diagnosis of an inherited translocation between chromosomes No. 9 and 18. J Med Genet 10:65-69, 1973

2. Fujimoto A, Towner JW, Turkel SB, et al: A fetus with recombinant chromosome 8 inherited from her carrier father. Hum Genet 40:241-248, 1978

3. The safety and accuracy of mid-trimester amniocentesis, USDHEW Pub No (NIH) 78-190. US Department of Health, Education, and Welfare, 1978

4. Carter CO, Evans KA: Risk of parents who have had one child with Down's syndrome (mongolism) having another child similarly affected. Lancet 2:785-788, 1961

5. Stein Z, Susser M, Guterman AV: Screening programme for prevention of Down's syndrome. Lancet 1:305-310, 1973

6. Broome DL, Wilson MG, Weiss B, et al: Needle puncture of fetus: A complication of second-trimester amniocentesis. Am J Obstet Gynecol 126:247-252, 1976

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The Relationship Between Genetics and Environment in the Pathogenesis of Rheumatic Diseases

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Major developments have taken place to further our understanding of the relationship between genetics and the environment in the pathogenesis of rheumatic disorders. The association between HLA markers and human disease is becoming clearer. For instance, HLA-DRW4 frequently occurs in patients with rheumatoid disease, and penicillamine and gold toxicity are seen most often in patients with HLA-DRW2 or DRW3. Antisera to B alloantigens help define the genetic differences between systemic lupus erythematosus and rheumatoid arthritis. As yet, the most dramatic link is that between HLA-B27 and primary ankylosing spondylitis. This same antigen is related, to varying degrees, with other members of the seronegative spondylarthritides and there is strong evidence that this association is related to HLA-B27, itself, rather than an associated disease gene. *Nevertheless, some data refute a single gene theory. We are just beginning to learn more about interactions between different genes on the sixth chromosome and genes on other chromosomes.*

The sex ratio of the spondylarthritides is now better defined. Sacroiliitis may have a comparable sex distribution although females have more peripheral joint disease and males have greater spinal involvement. Unfortunately, the explanation for these differences remains elusive.

The specific infective agents related to the development of rheumatic disorders are becoming clarified. Chlamydia, Salmonella, Yersinia and Shigella flexneri types 1b and 2a are arthritogenic, while Shigella sonnei appears not to cause disease. Although the Reiter syndrome is now considered a chronic disease, the reason for remissions and relapses remains unclear.

CHRONIC DISEASE often results from an interaction between the host and the environment. In the study of rheumatic disorders, geneticists and, in particular, immunogeneticists have made important strides in understanding host characteristics. At the same time, epidemiologists have begun to elucidate certain environmental factors. This review analyzes the relationship between genetics and the environment in the pathogenesis of rheumatic diseases.

Until recently, progress in rheumatology had

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been hampered by a lack of precise diagnostic definitions. Although we still suffer from ill-defined syndromes such as *seronegative rheumatoid arthritis* and the many forms of *degenerative joint disease,* there have been important developments in defining some seronegative arthritides in adults[1] and in children.[2]

Nurture and Nature

The relative contribution of nurture and nature varies for different rheumatologic conditions. For example, traumatic arthropathy can be considered entirely environmental in origin. In contrast, the Marfan syndrome is an autosomal dominant disorder with no environmental contribution. Most rheumatic conditions involve environmental and genetic factors in varying proportions. For example, the Reiter* syndrome may occur, preferentially, in patients with HLA (human leukocyte antigen)-B27, especially if these persons come into contact with a specific infective agent such as Shigella flexneri type 2a.

Certain disorders such as rheumatoid arthritis appear to be associated with specific HLA-DR antigens and, presumably, require unrecognized infective or other precipitating agents. Ill-defined diagnostic categories such as degenerative joint disease include numerous subsets which vary in their degree of genetic contribution and influence. For example, Heberden nodes, generalized postmenopausal osteoarthrosis and erosive osteoarthropathy are genetically related subsets, while degenerative disease of the first carpal metacarpal joint is predominantly determined by environmental factors. This review does not include heritable connective tissue disorders such as the Ehlers-Danlos syndrome (autosomal dominant) or arthropathies associated with autosomal recessive disease (for example, Wilson disease), X-linked recessive disorders (for example, hemophilia) or rare rheumatologic syndromes such as nail patella disease, a disorder that runs in families and is linked to one of the common blood groups (A, B or O).

Epidemiologic Studies

In general, the relationship between genetics and the environment in the pathogenesis of rheumatic diseases is evaluated by prevalence, racial, family and twin studies, together with analyses of age and sex distribution. In the past, analysis of blood group was of some help; now we can study HLA status and other genetic factors in patients with different rheumatic disorders.

TABLE 1.—*Explanation for Lack of Good Epidemiological Data on the Reiter Syndrome*

- No absolute diagnostic test
- Young adults: mobile community
- Venereal history suppressed
- Enteric features forgotten
- Clinically inapparent diagnostic features:
  - Silent mouth ulcers
  - Silent balanitis
  - Silent urethritis
- Nonspecific but clinically significant:
  - Eye disease
  - Skin disease
- Asymptomatic urethritis in females
- Asymptomatic cervicitis
- Misdiagnosis: seronegative rheumatoid arthritis
- Overlap between seronegative spondylarthritides (For example, the Reiter syndrome now considered ankylosing spondylitis)
- Fragmented care (a multisystem disorder)

In certain well-defined conditions, such as seropositive rheumatoid arthritis, epidemiologic studies are relatively simple to carry out. This disease is readily recognized in both sexes and its chronicity permits long-term studies. In contrast, prevalence and sex distribution data for the Reiter syndrome are virtually impossible to establish; some of the reasons for this difficulty are summarized in Table 1. There is no absolute diagnostic test, and reliance on long-term follow-up is hampered by the fact that the disease occurs in young adults who, by the nature of the disorder, form a mobile community. Not surprisingly, the important venereal history may be suppressed and possible enteric features forgotten. Such classic features as silent mouth ulcers and clinically inapparent balanitis may not be noticed by patient or physician, or may be self-limiting and no longer present when a patient's condition is evaluated. Nonspecific, though important, clinical features such as conjunctivitis, uveitis and keratodermia blennorrhagica may be mistaken for insignificant eye irritation or dermatitis. Moreover, many of these disease manifestations may antedate the arthropathy by months or years, sometimes clearing by the time the arthritic component develops. In women, the problem in diagnosis is compounded by the fact that urethritis and cervicitis are often clinically silent and frequently nonspecific.

For too long clinicians have relied on a catch-

*The WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

all diagnostic label, *seronegative rheumatoid arthritis,* for all nonspecific chronic inflammatory seronegative arthropathies. This term almost certainly includes many patients with ankylosing spondylitis, the Reiter syndrome and psoriatic arthropathy, the overlap between these entities further complicating the clinical features. Finally, many patients with the Reiter syndrome present to ophthalmologists, orthopedic surgeons, genitourinary specialists and others before an appropriate diagnosis is reached by a rheumatologist or other physician interested in the disease. Clearly, epidemiologic studies of the Reiter syndrome remain in their infancy because of a relative lack of clinical sophistication.

Prevalence Studies

Genetic as opposed to environmental influences can be studied by comparing the prevalence of a given disease within a population at large with that of first-degree relatives and nonconsanguinous household contacts. For example, the prevalence of gout is about 0.3 percent in a random white population, but rises to 6 percent in first-degree relatives of persons with the disorder.[3] Comparable figures for psoriatic arthropathy are about 0.1 percent and 5 percent, respectively.[4] Increased prevalence of ankylosing spondylitis among first-degree and second-degree relatives has long been recognized,[5] and the advent of HLA typing has clarified some, but not all, of these findings.

Sex Distribution

The sex ratio in rheumatic diseases is well defined in some disorders such as the Sjögren syndrome (9 females:1 male) and systemic lupus erythematosus (8 females:1 male), but is less clear in the B27-related disorders (Table 2). These sex differences may depend on hormonal modification, anatomy, the presence of the H-Y antigen[6] or other, as yet unidentified, sex-related factors.

Systemic Lupus Erythematosus: An Example

In contrast to psoriatic arthropathy or ankylosing spondylitis, disorders such as systemic lupus erythematosus have a plethora of serologic markers which make both genetic and environmental studies possible.[7] Evidence of environmental influences in the pathogenesis of systemic lupus includes the presence of anti-DNA antibodies in laboratory workers, antilymphocytic antibodies in spouses of patients, and immunoglobulin and complement deposition in skin biopsy specimens from spouses. Moreover, certain subsets of lupus are clearly drug related, procaine amide-induced lupus being the most easily recognized example. That homozygotic twins may be discordant for systemic lupus also attests to the essential influence of environmental factors.[7]

An association of hormonal factors with lupus is suggested by the strong preponderance of females with this disease, as well as by the apparent increase in prevalence among male patients with the Klinefelter syndrome (XXY chromosome abnormality). Of note, the strong preponderance of females with lupus is not found among children and persons over 50 years of age. Laboratory studies showing hormonal modulation of the autoimmune disease in New Zealand mice offer further evidence of a hormonal effect.[8]

The role of genetic influences is also evident in the findings of racial and other studies. Systemic lupus erythematosus develops three times more frequently in blacks than in whites.[7] The

TABLE 2.—*Sex Ratios in Rheumatic Diseases**

Disease	*Females:Males*
The Sjögren syndrome	9:1
Systemic lupus erythematosus	
In persons under 15 years old	3:1
In persons 15 to 30 years old	9:1
In persons over 50 years old	2:1
Rheumatoid arthritis	3:1
Polymyositis	3:1
Polymyalgia rheumatica	2:1
Scleroderma	3:2
Polyarteritis nodosa	1:2
Gout	1:10
Pseudogout	1:1
Ankylosing spondylitis:	
Severe spinal disease	1:5
Clinical ankylosing spondylitis	1:3
Sacroiliitis	1:1
Sacroiliitis and peripheral arthropathy†	2:1
The Reiter syndrome:	
Nonspecific urethritis	1:5
Postvenereal Reiter syndrome	1:10
Shigellosis	1:1
Post-Shigella Reiter syndrome	1:1
Yersinosis	1:1
Yersinia arthropathy	1:1
Yersinia arthropathy and erythema nodosum	10:1

*Differences related to hormones, anatomy, the H-Y antigen or other factors.

†Dequeker J, Decock T, Walravens M, et al: A systematic survey of the HLA B27 prevalence in inflammatory rheumatic diseases. J Rheumatol 5:452-459, 1978.

prevalence of lupus in a random population is about 1:1,000 to 1:10,000. In contrast, this disease develops in 1 percent to 2 percent of first-degree relatives.[7] Concordance among dizygotic twins provides similar figures,[7] while concordance for lupus among monozygotic twins occurs in 60 percent of the persons studied. Moreover, the prevalence of antinuclear factor (about 70 percent) and hypergammaglobulinanemia (85 percent) in monozygotic twins is evidence of the genetic contribution.[7] Recently, studies of HLA have suggested a link between lupus and HLA-B8 in whites and HLA-BW15 in blacks, and more specifically with HLA-DRW2 and DRW3 (relative risk of 3.7 and 3.0, respectively). Of major interest has been the description of a serum (Ia715) that was identified in 76 percent of lupus patients compared with 14 percent of controls (a relative risk of 19).[9] The link between C2 deficiency and lupus is well known[10] as is the association between slow acetylator status and drug-induced lupus.[11] The gene coding for C2 is found on the sixth chromosome, near the HLA-DR region, a finding that may explain the association between C2 deficiency and lupus.

The Histocompatibility Antigen System

The HLA gene-complex region of the sixth chromosome in humans is shown in Figure 1, and examples of disease associations are listed below each locus. The more important associations are with the HLA-B, D and DR loci. The HLA-A, B, C and DR antigens are coded for by four genes in the HLA region. The A, B and C antigens can be shown to be present by complement-mediated lymphocytotoxicity on peripheral blood lymphocytes and DR antigens shown on B lymphocytes derived from bone marrow.[12] The term DR (D related) replaces the older Ia nomenclature (immune associated). The HLA-A, B and C antigens are glycoproteins occurring on the surface of cells which consist of a light chain (molecular weight 12,000), a $\beta 2$ microglobulin, which is coded for by a gene on chromosome 15, and a heavy chain (molecular weight 43,000) which bears the antigenic terminal that confers HLA specificity on the molecule and is a product of the HLA-A, B and C loci. The HLA-DRW (W = workshop) antigens are also composed of dissimilar polypeptides, one with a molecular weight of 33,000 and the other of 28,000. The biologic relevance of the HLA-DR alloantigen system remains unclear. By extrapolating data from studies in mice, it may be that the antigens are associated with immune response genes. The DRW antigens are coded for by the HLA-D(R) locus which is either identical to or very closely related to the HLA-D locus that determines the lymphocyte-defined (by mixed lymphocyte culture) HLA-D antigens. To date, 20 HLA-A specificities have been identified, as have been 33 B, 6 C, 11 D and 7 DR alleles. Some of the A and B antigens, and all of the C, D and DR antigens are designated with the letter *W* followed by their appropriate number. For example, rheumatoid arthritis is associated with DW4 and DRW4. In the future, if the monospecific nature of the antigen is agreed upon, the suffix *W* will be dropped, as has already happened with HLA-B(W)27.

The functions controlled by genes in the HLA region have recently been reviewed.[12,13] They include the specificities mentioned above, as well as development of complement components, cell-cell recognition and possibly other activities. The classic *autoimmune* disorders such as myasthenia gravis, chronic active hepatitis, Addison disease, thyrotoxicosis and insulin-dependent diabetes

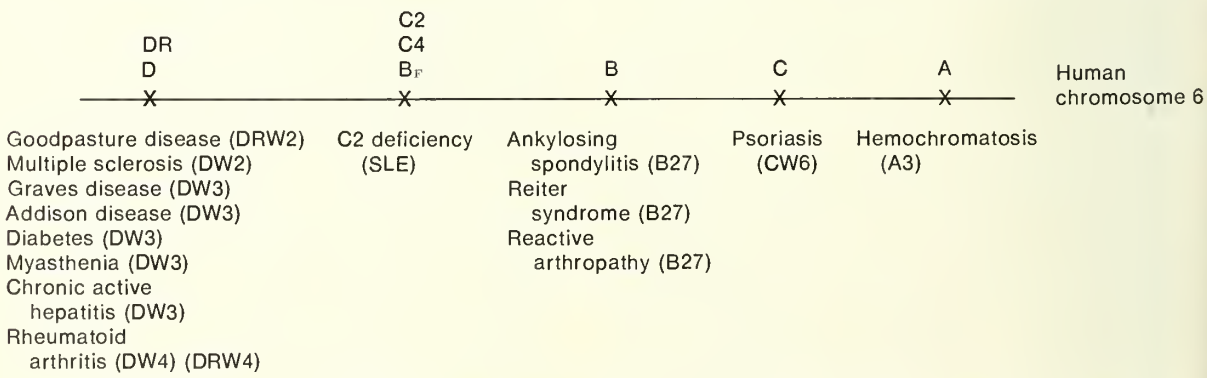

Figure 1.—HLA gene-complex region of human chromosome 6 with examples of disease associations listed below each locus.

mellitus are HLA-B8 associated. These diseases all have the propensity to develop autoantibodies directed at self (or intrinsic) antigens. In contrast, HLA-B8 is also linked with disorders such as gluten-sensitive enteropathy and enhanced graft rejection, conditions associated with antibodies directed toward extrinsic antigens.[12] Therefore, there is evidence for an HLA-linked gene responsible for nonspecific increase of antigens in immune responsiveness. Clearly, disease specificity must reside in other HLA or non-HLA-linked genes or result from poorly recognized environmental influences.

There is some evidence that persons with HLA-B8 are high responders. For example, those with HLA-B8 tend to have rapid clearance of hepatitis B surface antigen (HBsAg) and high-titer antibodies to rubella, measles, muscle and nuclear antigens in conditions such as hepatitis, and anti-insulin and antipancreatic cell antibodies in diabetes.[14] Furthermore, B8-positive patients with coeliac disease have higher frequencies of antibodies to gluten than do their B8-negative counterparts. In contrast, persons with HLA-B7 are low responders. Patients with thyrotoxicosis who are B7 positive tend to have low titers of anti-thyroid globulin and antimicrosome antibody, and B7-positive patients with insulin-dependent diabetes have low-titer anti-insulin antibodies.[12] Further, it has been suggested that there may be a protective effect of HLA-B7 in diabetes and coeliac disease. The effect of HLA-B8 (in linkage disequilibrium with DRW3) acting as a *high-risk* gene in conjunction with HLA-B15, in contrast to HLA-B7 (in linkage disequilibrium with DRW2) acting as a *low-risk* gene in the pathogenesis of juvenile diabetes mellitus[15] will be discussed below.

The Genetics of Rheumatoid Arthritis

Clinical Background

Is rheumatoid arthritis a single disease or a spectrum of unrelated disorders? Only during the last decade have the seronegative spondylarthritides been clearly distinguished from seropositive rheumatoid arthritis.[1] Indeed, these disorders (with ankylosing spondylitis as the prototype) may be differentiated from rheumatoid disease on historical, epidemiologic, geographic, ethnic, sex, age, clinical, pathologic, radiologic, immunologic, immunogenetic, serologic and even therapeutic grounds.[16] But what of seronegative rheumatoid arthritis? Clearly, in some patients, diseases given this diagnostic label (especially in those patients seen early in the course of their illnesses), will become seropositive later. Those with occult psoriasis (scalp, gluteal fold and periumbilical region) or sacroiliitis should be considered as having a seronegative spondylarthropathy (psoriatic arthropathy or ankylosing spondylitis). Persons in whom psoriasis develops later may have *psoriatic arthritis sine psoriasis*. This concept is useful for patients with an asymmetric arthropathy, dactylitis or, perhaps, family history of psoriasis.

The difficulty in recognizing the Reiter syndrome has been discussed. The onset of arthropathy in childhood probably involves a different disease process than for the adult seronegative disease. Certainly, it is just as naive to consider all seronegative rheumatoid arthritis a single disease as it is to lump together all arthritic disorders occurring in children as *juvenile rheumatoid arthritis*. We now recognize that the latter group of disorders falls into several well-defined subsets. It is probable that the same clarification will occur for this spectrum of diseases as with those occurring in adults. We should consider that patients have a *seronegative inflammatory polyarthropathy of unknown classification* rather than use the unrealistic and emotive term seronegative rheumatoid arthritis. In the interim, we cannot expect successfully to identify clear-cut genetic and environmental influences if we lump all of these diseases together as seronegative rheumatoid arthritis.

Despite the absence of environmental clues we have some tantalizing genetic findings regarding seropositive disease. It is generally considered that the prevalence of rheumatoid arthritis is about 1 percent;[17] in contrast, the prevalence among first-degree relatives is between 3 percent and 8 percent.[18] For decades, patients have told us that their rheumatoid arthritis "runs in families."

Immunogenetics

An initial search for a relationship between HLA-A, B and C antigens failed to show a link between the HLA region of chromosome 6 and rheumatoid disease. More recently, however, an association between HLA-D (and DR antigens) and rheumatoid arthritis has been determined.[19-22] This association was considered unique because no previous disorder had been linked to the D locus in the absence of any A, B or C association;

now another rheumatologic disorder, Goodpasture disease, has been linked with HLA-DRW2 in the absence of other HLA associations.

Initially, Stastny showed an association between HLA-DW4 and rheumatoid arthritis.[19] Of the patients in the study, 59 percent were DW4 positive while only 16 percent of the controls were positive. Later, McMichael and colleagues showed a similar link; their figures were 36 percent and 13 percent, respectively.[20] Thereafter, an association with DRW4 was found.[21,22] Of the patients, 70 percent were DRW4 positive in contrast to 28 percent of controls. Of interest, the DW4 relationship was found only in whites; only 14 percent of American blacks and 10 percent of Mexican-Americans with rheumatoid arthritis were DW4 positive,[19] indicating the need to study this association within different ethnic groups. A similar difference will be noted in the discussion on ankylosing spondylitis and the other spondylarthritides.

More recently, results of a study in London showed the presence of DRW4 in 34 percent of controls and in 56 percent of patients with rheumatoid disease.[22] Allowing for appropriate statistical corrections, there was a decrease in prevalence of DRW2 within the patient population; only 14 percent of the subjects were positive in contrast to 30 percent of controls. Furthermore, patients with rheumatoid arthritis and DRW2 were considered to have milder disease with lower titers of rheumatoid factor. The prevalence of nodules was also less. Therefore, DRW2 appears to protect persons from developing rheumatoid arthritis, but if the disease does occur it is less severe. DRW2 is in linkage disequilibrium with HLA-B7. As discussed earlier, HLA-B7-positive patients with autoimmune disorders tend to have low-titer antibodies to both intrinsic and extrinsic antigens.[12] Moreover, the protection of HLA-B7 and DRW2 has been discussed in relationship to insulin dependent diabetes.

In the same London study,[22] the findings showed that HLA-DRW3 was present in 30 percent of patients with rheumatoid arthritis and 27 percent of controls, a comparable distribution. However, patients with DRW3 tended to have stronger rheumatoid-factor seropositivity. This finding is correlated with the association between DRW3 (and HLA-B8, in linkage disequilibrium) and autoimmune disorders with enhanced autoantibody activity. For example, patients with chronic active hepatitis and HLA-B8 have higher antinuclear and antismooth muscle antibody titers than their B8-negative counterparts.[14]

Of particular interest was the suggestion that toxic reactions to gold and penicillamine occurred more frequently in rheumatoid arthritis patients with HLA-DRW2 or DRW3 compared with patients with other DRW antigens. Although these subsets were small and appropriate statistical corrections were not made, the possibility that drug toxicity may be genetically determined does not seem unreasonable. In some cases drug toxicity may be immunologically determined and an HLA-linked immune response mechanism appears possible. In general, it is recognized that penicillamine is relatively nontoxic in patients with Wilson disease when compared with those with rheumatoid arthritis. Moreover, penicillamine is administered in higher doses to patients with the former disease. Likewise, levamisole has been used for many years as an antihelmintic agent and was considered relatively nontoxic in these infective disorders. Now, bone marrow toxicity is seen relatively frequently in patients with rheumatoid arthritis, suggesting that certain host characteristics influence the degree of toxicity. Some investigators have suggested that levamisole is particularly toxic in HLA-B27-positive patients with rheumatoid arthritis. They have recommended that patients with this disease should be HLA typed before levamisole is given.[23] The suggestion that drug-induced systemic lupus is more apt to develop in patients who are slow acetylators than in their fast acetylator counterparts[11] was discussed above. No doubt HLA and non-HLA-linked genetic mechanisms that apparently influence drug tolerance should be studied further.

The Genetics of the Seronegative Spondylarthritides

Clinical Background

Spondylarthropathies should not be considered *rheumatoid variants*. The term is derived from the fact that these seronegative arthropathies have both spinal and peripheral joint involvement. The group includes the prototype, ankylosing spondylitis, as well as the Reiter syndrome, the spondylitic syndrome associated with inflammatory bowel disease, certain subsets of juvenile chronic polyarthropathy, the reactive arthritides (Salmonella, Yersinia and Shigella), psoriatic arthropathy and, possibly, Whipple disease and the Beh-

TABLE 3.—*Distribution of HLA-B27 in Different Healthy Populations*

Population	*Percent*
Aborigines	<1
Japanese	<1
Blacks:	
Africa	<1
United States	4
Whites:	
Great Britain	6-8
Scandinavia	10-14
North American Indians:	
Pima	18
Haida	50

cet syndrome. These conditions are interrelated at personal and familial levels. For example, sacroiliitis may develop in patients with inflammatory bowel disease or the Reiter syndrome and uveitis or spondylitis may develop in persons with psoriatic or Yersinia arthropathy. Moreover, patients with the Reiter syndrome are more likely to have relatives with psoriatic arthropathy or ankylosing spondylitis than would be expected to occur by chance alone; this increased prevalence of spondylitis among family members of probands with any of the spondylarthritides has been well recognized.

Immunogenetics

No HLA association is as close as that between HLA-B27 and the spondylarthropathies. Since 1973, when two groups of investigators described the link between HLA-B27 and ankylosing spondylitis,[24,25] there have been numerous articles published in which the association between HLA antigens and the group of related disorders that form the seronegative spondylarthritides has been analyzed. The distribution of HLA-B27 in different healthy populations is summarized in Table 3 and the frequency of the antigen in different rheumatic diseases is given in Table 4.

It has long been recognized that ankylosing spondylitis is more frequently seen in whites than in certain other races. For example, the disease is unknown in African blacks, very rare in Asians and seen less frequently in American blacks than whites.[26,27] These different ethnic prevalences are now recognized to follow the distribution of HLA-B27 in the normal population. For instance, HLA-B27 is present in less than 1 percent of Japanese[28] and African blacks, in 3 percent to 4 percent of blacks in the United States[29] (the difference due, in part, to racial admixture) and in 6 percent to 14 percent of whites. The highest known prevalence of B27 is in the Haida Indians[30] of British Columbia. About half the males tested are B27 positive and about 20 percent of these have sacroiliitis.

TABLE 4.—*HLA-B27 and Rheumatic Disease**

Disease	*Percent HLA-B27 Positive*
Ankylosing spondylitis†	90-100
Endemic Reiter syndrome‡	70-90
Psoriasis	5-10
Psoriatic arthropathy without sacroiliitis	18-22
Psoriatic arthropathy with sacroiliitis	50-60
Seropositive juvenile rheumatoid arthritis	7-10
Juvenile chronic polyarthropathy without sacroiliitis	15-25
Juvenile chronic polyarthropathy with sacroiliitis	40-60
Inflammatory bowel disease	5-10
Inflammatory bowel disease with peripheral arthropathy	5-10
Inflammatory bowel disease with sacroiliitis	50-70
Yersinia infection	5-10
Yersinia-reactive arthropathy	80
Salmonellosis	5-10
Salmonella-reactive arthropathy	80-90
Shigellosis	5-10
Post-Shigella arthropathy (epidemic Reiter syndrome)	80
Uveitis	40-50
Chronic balanitis	90
Rubella arthritis	5-10

*Modified and reproduced by permission of the publisher. From Calin A, Fries J: Ankylosing Spondylitis: Discussions in Patient Management. Garden City, NY, Medical Examination Publishing Company, Inc, Feb 1978.

†Japanese and blacks: 60 percent; Pima Indians, males: 50 percent; females: 10 percent.

‡Blacks: 60 percent.

Psoriasis, inflammatory bowel disease, yersinosis, shigellosis and salmonellosis are not B27 associated.[31] The prevalence of B27 in these disorders reflects that in the general population. However, as seen in Table 4, the arthropathies associated with the infections mentioned above are B27 associated, as are spinal manifestations of inflammatory bowel disease, psoriatic arthropathy and juvenile chronic polyarthropathy.[27] Some studies have suggested an increased prevalence of HLA-B27 in the last two disorders even in the absence of sacroiliitis. Of interest, HLA-B27 has been found present in only half of patients with psoriatic arthropathy or inflammatory bowel disease complicated by sacroiliitis. It seems, therefore, that the genetic influence of HLA-B27 is less necessary in the presence of psoriasis or in-

flammatory bowel disease. Conceivably, other genetic or environmental processes are also interacting with these primary disorders.

Apart from male Haida Indians, the association between HLA-B27 and ankylosing spondylitis is weaker in nonwhite populations. Only about 66 percent of Japanese[28] and 50 percent of American blacks[29] with the disease are HLA-B27 positive. The reason for this varying association may be related to the fact that B27, itself, is not the disease gene, but rather a marker for a specific disease-associated gene that is in varying linkage disequilibrium with B27 in different ethnic groups.

Our studies of the Pima Indians[32] have posed a further problem. HLA-B27 is present in 18 percent of healthy Pima Indians but in 57 percent of males with sacroiliitis. In contrast, the prevalence of B27 among female Pima Indians with sacroiliitis is only 10 percent. Overall, the prevalence of sacroiliitis is striking in both sexes; 15 percent of male and 24 percent of female Pima Indians have sacroiliitis. As is true in whites, uveitis occurs predominantly in those with sacroiliitis. The apparent lack of association between HLA-B27 and sacroiliitis in female Pima Indians cannot be explained.

The clinical situation is further complicated by the fact that different *formes frustes* of seronegative spondylarthritides are associated in varying degrees with B27. For example, balanitis alone[33] may be B27 related and reports of dactylitis, uveitis, calcaneodynia, seronegative oligoarthropathy and even shoulder capsulitis occurring in B27-positive subjects have appeared.[34] Other studies are needed to confirm these associations. Meanwhile, it remains uncertain as to why and how such disparate conditions can occur in one person—that is, in a single genetic situation. We followed up four patients with balanitis, all with HLA-B27, for two or three years before a classic picture of Reiter disease developed. These B27-associated *formes frustes* remind us that our diagnostic classification of these cases is often empirical, and we sometimes lump together or divide them incorrectly. Nevertheless, HLA-B27 has helped in understanding nosologic clustering on the one hand (ankylosing spondylitis, the Reiter syndrome, juvenile ankylosing spondylitis and psoriatic spondylitis) and subdivision or subsetting on the other (for instance, juvenile rheumatoid arthritis consists of various subsets, one of which being B27-related oligoarthropathy).

The effect of gene dosage is not clear. For example, myasthenia gravis, chronic active hepatitis and diabetes mellitus may occur more frequently in the HLA-B8-homozygous person.[15] In contrast, B27-related disorders probably occur with equal prevalence in the B27 homozygote or heterozygote. As a corollary, the prevalence of B27 homozygosity among a group of spondylitics is comparable to that among a control population. It has been suggested that homozygosity for B27 results in more severe disease,[35] however, such reports may reflect publication bias rather than actual fact. The consensus is that no definite effects based on gene dosage have been shown in rheumatologic disorders.

The Risk to HLA-B27-Positive Persons

In 1975, we showed that about 20 percent of HLA-B27-positive blood donors had symptomatic sacroiliitis regardless of gender.[36] At the same time, findings from a study of B27-positive male blood donors showed a comparable prevalence of *spondylitic stigmata*.[37] Other studies[38-40] as well as our experience with the Pima Indians[32] have provided similar figures. If in 20 percent of HLA-B27-positive persons symptomatic sacroiliitis (ankylosing spondylitis) develops without obvious environmental insult, then about 1 percent of all whites will have the disease. This figure is much greater than the often quoted ratios of 1:1,000 for males and 1:10,000 for females. It is clear that in most persons with ankylosing spondylitis the condition is unrecognized. Certainly, many persons with this disease are misdiagnosed, and therefore undergo inappropriate testing procedures (for example, myelograms) and treatment (such as bedrest or laminectomies). Radiologists and physicians must appreciate that ankylosing spondylitis may be diagnosed in the presence of minimal sacroiliitis. Total loss of the sacroiliac joints or spinal involvement is unnecessary for a diagnosis to be reached. It is hoped that with increased awareness of and interest in the HLA-B27-related disorders by physicians, the misdiagnosed and mismanaged spondylitic condition will soon be a phenomenon of the past.

As mentioned, many older texts suggested that ankylosing spondylitis occurs ten times more frequently in men than women. This claim results in a delay and reluctance to diagnose the condition in women.[41] Moreover, women with ankylosing spondylitis tend to have more peripheral joint involvement and less severe spinal disease than men.[42] Therefore, this spondylitic condition

in women was often diagnosed as seronegative rheumatoid arthritis. A more accurate ratio based on gender is two or three males to one female. What is the explanation for this sex difference? Why do women have more peripheral joint involvement? These and other questions remain unanswered. As suggested, the difference may be explained in part by lack of clinical sophistication, but other factors are certainly relevant.

A reactive arthropathy or typical triad of the Reiter syndrome (arthropathy, inflammatory eye disease and urethritis) following nonspecific urethritis or a definitive infective episode (such as yersiniosis, salmonellosis or shigellosis) develops in about 20 percent of HLA-B27-positive persons. Whether the same 20 percent of HLA-B27-positive persons are at risk for ankylosing spondylitis occurring following an unknown event or the Reiter syndrome developing following a specific infection remains unknown.

Of interest, according to J. P. Gofton, MD, (unpublished observation, 1978) and P. H. Bennett, MD, (unpublished observation, 1978) ankylosing spondylitis is apt to develop in certain populations such as the Pima and Haida Indians and North African Arabs (B. Amor, MD, unpublished data, 1978), while Reiter syndrome is rarely seen in these ethnic groups. Because the infective precipitating agents are mostly ubiquitous, it may be that American Indians and Arabs are *immune* to the relevant infectious agent that has been present since childhood.

Etiology of Ankylosing Spondylitis

HLA Data

In trying to identify environmental factors that may trigger ankylosing spondylitis, we have discovered the following clues: (1) At least 90 percent of white patients with primary disease (that is, in the absence of psoriatic arthropathy, the Reiter syndrome or inflammatory bowel disease) carry the antigen HLA-B27.[24,25] (2) Although sacroiliitis may occur with equal prevalence in both sexes, the disease tends to be more severe in males. (3) There appears to be no association between ankylosing spondylitis and the HLA-D or DR region.[43] This striking finding is in contrast to most other disorders where the primary association is with the D region. (4) A secondary form of spondylitis may develop in patients with post-Shigella (and other infective) arthropathies. (5) The disease is found in populations in most geographic areas, but is more common in those ethnic groups with a higher prevalence of HLA-B27 (6) Nonwhites are less frequently B27 positive than their white counterparts. (7) This disease tends to develop in persons during their early decades.

Results of a recent study from Iceland suggested that ankylosing spondylitis is more likely to develop in persons with both HLA-B27 and the B_FS allele of properdin B factor (alternative complement pathway) than in persons with B27 and the B_FF allele.[44] Because the B_F locus is situated on the D side of the B locus on the sixth chromosome, the disease gene, if not HLA-B27 itself, appears to be located between HLA-B and D. However, these findings were not confirmed in an Italian study.[45] Previous investigations have suggested that ankylosing spondylitis is more likely to develop in persons with HLA-A2 and B27 than in HLA-A2-negative persons.[46] It also appears that there is a greater risk that ankylosing spondylitis develops in persons with HLA-A28 and B27 than in A28-negative persons.[47,48] In this instance, the disease gene would be located on the HLA-A side of the B locus. The situation is further confused by two conflicting reports, one incriminating HLA-CW1 and CW2 in the pathogenesis of spondylarthropathies[49] and the other refuting this suggestion.[50] In essence, the debate as to whether HLA-B27, itself, or a nearby disease-specific gene is relevant in the pathogenesis of ankylosing spondylitis continues.

The Single-Gene Theory (B27 Itself)

The hypothesis that HLA-B27 itself is instrumental in the pathogenesis of ankylosing spondylitis (that is, a single-gene effect) has received support for several reasons. There is no HLA-D link in spondylitis,[43] and the very high association between B27 and the disease suggests that B27 itself is of paramount importance. Moreover, certain studies have suggested that even in the absence of HLA-B27, one of the cross-reacting antigens (HLA-B7, B22 or BW42) is present.[51] Because these antigens may appear *similar* to the putative infective agent, the disease may develop regardless of which of the cross-reacting antigens is present. It is postulated that the infective agent, not recognized as foreign by the host, may replicate and cause disease (cross-tolerance) or that the body mistakes the infective agent for self-tissue and destroys both the self-tissue and the

invading offender (molecular mimicry).[52] As an example, acute rheumatic fever may result from molecular mimicry; the host antibodies cross-react with the streptococcal M antigen and cardiac tissue. The fact that B27 is associated with disease in different ethnic groups is an additional argument in favor of the role of B27 itself. This situation contrasts with the finding in thyrotoxicosis. Whites are HLA-B8 positive while Japanese are B5 positive.[53] In this situation, it is postulated that B8 and B5 occur in linkage disequilibrium with the appropriate disease gene in the two ethnic groups, respectively. Finally, the suggestion that Klebsiella cross-reacts with HLA-B27 provides further support for the role of B27 itself.[54,55]

The Disease-Associated Gene Theory (Second Gene)

The alternative theory, stating that B27 is merely a marker for a specific disease-associated gene, has received limited support. In non-B27-related disorders, the D association is usually greater than the B association, suggesting that the disease gene is in the HLA-D region. After extrapolating data from animal studies,[52] investigators have considered that this area may include immune-response genes. This theory is best suited to those disorders that are clearly autoimmune. There is now increasing evidence that ankylosing spondylitis and the Reiter syndrome are not the immunologically silent disorders that they appeared to be.[56] Thus, there may be an HLA-linked immune-response gene related to the pathogenesis of these disorders. Moreover, results of studies have shown that it is more likely that the Reiter syndrome rather than ankylosing spondylitis will develop in persons with HLA-A3-B27.[46] If this is true, it suggests that the haplotype is relevant in disease pathogenesis rather than the specific antigen, B27 itself. Also, varying degrees of association between HLA and disease in different ethnic groups (such as Japanese, Pima Indians, blacks and whites) suggest that HLA-B27 may occur in differing linkage disequilibrium with the specific disease-associated gene. Finally, the fact that ankylosing spondylitis can occur in persons in whom there is an absence of HLA-B27 needs to be explained. In fact, such a condition is rarely found in the absence of one of the cross-reacting antigens or a primary disorder such as psoriatic arthropathy or the Reiter syndrome.

Findings from some family studies have shown that HLA-B27-positive persons who are healthy can be related to HLA-B27-negative patients with ankylosing spondylitis. This supports the second theory; the inference being that a cross-over has occurred between B27 and the disease gene itself. Finally, B27 is associated with different diseases, and therefore may be a marker for different disease genes (for example, ankylosing spondylitis or the Reiter syndrome).

In summary, different mechanisms are probably required to explain these various disease associations.[52]

Non-HLA Gene Contributions and Genetic-System Interactions

The situation is complicated still further by the fact that non-HLA-related genes may also be involved in the pathogenesis of rheumatic diseases. For example, HLA-DW4 (on chromosome 6) and the MZ phenotype of alpha-1 antitrypsin (on a different chromosome) may interact in the pathogenesis of rheumatoid arthritis and fibrosing alveolitis.[57] Similarly, the MZ phenotype and HLA-B27 are associated more frequently than would be expected by chance alone in ankylosing spondylitis and uveitis.[58] No doubt, other interactions between different genetic systems will be clarified in the future.

The Search for Infective Agents

The fact that monozygotic twins may be discordant for ankylosing spondylitis[59] is proof of the necessity for environmental trigger factor(s). A report incriminating Klebsiella in the pathogenesis of ankylosing spondylitis[54] has not received bacteriologic support from other investigators.[60,61]

However, recent evidence[57] suggesting that Klebsiella antigens do cross-react with a gene product closely associated with HLA-B27 or with Klebsiella-associated B27 antigen, adds credence to the earlier observation.[54] Because the Reiter syndrome may be caused by several infective agents (for example, Shigella and Salmonella) it seems possible that more than one organism may precipitate ankylosing spondylitis in a susceptible host. Moreover, because ankylosing spondylitis occurs with an appreciable prevalence (20 percent of all B27 subjects), regardless of geographic location, it appears that the infective agent is ubiquitous, or that many different organisms or toxins are involved.

The Reiter Syndrome: Genetics Versus Environment

The Reiter syndrome is provocative for rheumatologists because a clearly defined infection (for example, Shigella) in the presence of a specific genetic background (HLA-B27) leads to a chronic rheumatic disease (the Reiter syndrome). The recognized infective events in the pathogenesis of Reiter disease include both venereal and enteric infections. It is important to note that urethritis, per se, may be either the precipitating infective event or a noninfective manifestation of a primary dysenteric (infective) bowel process.[62]

Venereally Acquired (Endemic) Reiter Syndrome

Nonspecific urethritis, as a precipitating event, may be caused by Chlamydia[63] in about 30 percent to 40 percent of cases, by Ureaplasma urealyticum (formerly called T strains of mycoplasma) in some patients and by unrecognized infective agents in the remaining patients.[64] In between 1 percent and 3 percent of persons who present with nonspecific urethritis, a partial form, the full triad or more features of the Reiter syndrome will develop.[65,66] Extrapolating from incidence figures of Csonka,[65] Laird[66] and other investigators, and knowing the prevalence of HLA-B27 in these communities, it appears that nonspecific urethritis will progress to Reiter disease in about 20 percent of HLA-B27-positive patients. The similarity between this 20 percent figure and that mentioned for ankylosing spondylitis is striking.

It remains unclear whether Ureaplasma urealyticum causes the Reiter syndrome, but Chlamydia has been incriminated as a precipitating agent in studies carried out in London[63] and California.[67] The London investigators showed that 36 percent of patients with nonspecific urethritis had positive cultures for Chlamydia as did 43 percent of persons with "sexually acquired reactive arthritis." More specifically, 50 percent of the former group had increased titers of IgG antibody to Chlamydia (greater than 1:16) compared with 73 percent of patients with reactive arthropathy. Control figures include 10 percent for rheumatoid arthritis, 23 percent for lupus, 13 percent for ankylosing spondylitis and 10 percent for healthy subjects. The geometric mean titers for the nonspecific urethritis and reactive arthropathy patients were 7.8 and 42.2, respectively. This striking difference was not related to the B27 status of the arthropathy subjects. These findings suggest that there are different host responses to Chlamydia in those persons in whom arthropathies later develop compared with those in whom only nonspecific urethritis will develop.[68] The responsible agent for the development of venereally acquired Reiter syndrome in those patients without evidence of chlamydial infection remains unclear. Likewise, what determines whether patients will have a limited form of the Reiter syndrome, the full triad or more features also remains uncertain. The effect of HLA-B27 is discussed below.

Postdysenteric (Epidemic) Reiter Syndrome

Shigella, Salmonella and Yersinia infections are associated with the Reiter syndrome in 1 percent to 4 percent of patients. Again, the risk for an HLA-B27-positive person in whom one of these enteric infections develops appears to be in the range of 20 percent to 30 percent. These figures are derived from our own follow-up study[69] of post-Shigella Reiter syndrome and Scandinavian experience with Salmonella typhimurium[70,71] and Yersinia.[72,73]

In an attempt to carry out prospective studies we evaluated Shigella flexneri types 1b and 2a and Shigella sonnei epidemics in the United States. In a controlled study[74] we confirmed that S. flexneri type 2a was arthritogenic,[75] that S. flexneri type 1b caused Reiter disease and that S. sonnei was not associated with the Reiter syndrome.[74] Of interest, again, in about 20 percent of B27-positive subjects Reiter disease developed after contact with the arthritogenic agent.

In addition to Shigella, Yersinia and Salmonella, other infective agents may cause a similar disease. For example, reports[76,77] have incriminated Campylobacter fetus jejuni in the pathogenesis of the Reiter syndrome.

The Sex Ratio of the Reiter Syndrome

In contrast to the apparent sex ratio of 10:1 in favor of male patients with the postnonspecific urethritis form of the disease, the sex ratio of post-Yersinia, Salmonella and Shigella arthritis is equal. Because the Reiter syndrome is difficult to recognize in women, the 10:1 ratio may be exaggerated. Moreover, it is likely that nonspecific urethritis, itself, occurs more frequently in males than females (perhaps 5:1), so it may be that the initial infection rather than the resulting rheumatic syndrome is sex related. In our own experi-

ence with the epidemic form of the disease, the syndrome developed in more women than men.[74]

In conjunction with membrane biologists, we are carrying out studies to analyze the nature of arthritogenic and nonarthritogenic Shigella strains in an attempt to define the specific arthritogenic component in the bacterial cell wall.

The Effect of HLA Status on Disease Severity

The severity of ankylosing spondylitis in HLA-B27-positive and HLA-B27-negative patients appears to be comparable. In contrast, results of previous studies have suggested that Yersinia arthropathy,[73] endemic Reiter syndrome[78] and post-Shigella disease[69] are more severe in HLA-B27-positive patients than in their negative counterparts. However, in our own experience of 131 consecutive cases of the Reiter syndrome (four fifths of the patients had the nonspecific urethritis form of the disease), there appeared to be no difference between the HLA-B27-positive and HLA-B27-negative subjects,[79] apart from an increased prevalence of eye and spinal disease in HLA-B27-positive subjects. About 80 percent of our patients were B27 positive. The chronicity of the Reiter syndrome is also apparent in this study. At follow-up at a mean of 5.6 years, 85 percent of consecutive patients had active disease ranging from minimal symptoms to major disability. This attests to the importance of the Reiter syndrome as a chronic rheumatic disorder.

Psoriatic Arthropathy and HLA

We have recently described a pair of monozygotic twins discordant for psoriatic arthropathy.[80] The twins are now 67 years old and the affected twin has had severe skin disease and arthropathy for almost 50 years. Clearly, an environmental factor must have precipitated the disease in the affected brother. Psoriasis itself appears to have multiple associated genes[81] and a gene-dependent, age-related onset. Patients less than 20 years of age are more likely to have BW17 while older patients have BW16. The closest association between psoriasis and HLA incriminates a CW specificity (CW6).[12] HLA-BW38 occurs more frequently in patients with psoriatic arthropathy than in a control psoriatic population.[82] The relationship between the skin disease, peripheral arthropathy and spondylitic manifestation remains unclear.

Other Infections and Rheumatic Disease

In view of the recognized defects in host-defense mechanisms that may predispose to infection,[83] it is surprising that there are no further associations between specific infective arthropathies and HLA. Poststreptococcal rheumatic fever is not related to HLA-B27, and its possible associations with other HLA antigens are controversial. One recent study[84] suggested a modest increase in BW35 and decrease in B5. This latter observation is of interest because persons with HLA-B5 are more likely to have increased *in vitro* responses to streptococcal antigens.[85]

The arthropathy following natural rubella or vaccination is not B27 associated, and no other specific deviations have been described.[86] Four clinically distinct rheumatologic syndromes are associated with hepatitis B virus.[87] These include a transient, symmetrical polyarthritis occurring as a prodrome of icteric or anicteric acute hepatitis B, a similar arthropathy seen during the course of chronic active hepatitis, a polyarteritis occurring in patients with HBsAg, and the recently described association between hepatitis B and *essential* mixed cryoglobulinemia. To date, no genetic studies of these disorders in large numbers of persons have been carried out. However, it is likely that genetically determined differences in host response predispose to different clinical syndromes. Inman recently reviewed the effects of gender and response to infection.[88] The difference in how male and female patients respond to the hepatitis B antigen may be related to the different rheumatic syndromes that result from hepatitis B infection.

Polymyalgia Rheumatica and Temporal Arteritis

Increases in HLA-B5 and BW38 have been reported in patients with polymyalgia rheumatica, particularly in those subjects who also had temporal arteritis, but not in those with temporal arteritis alone. If confirmed, it would appear that polymyalgia rheumatica and temporal arteritis are distinct entities or that polymyalgia rheumatica is more likely to develop in patients with temporal arteritis and B5 or BW38.[89]

Vertebral Ankylosing Hyperostosis and Osteitis Condensans Ilii

At one time it was considered that vertebral hyperostosis was associated with HLA-B27.[90] This led to the supposition that B27 might be associated with a propensity to develop new bone. Further studies, however, have not confirmed this association.[91] That osteitis condensans

ilii is a condition unrelated to ankylosing spondylitis has been confirmed by the absence of B27.[92]

Behcet Disease

There is a suggestion that Behcet disease may be infective in origin.[93] In patients in Japan, an association between this disease and HLA-B5 has been noted.[94] In contrast, no such association was found in patients in Great Britain in whom there is a weak link between Behcet disease and B27.[95]

The Sjögren Syndrome

HLA-B8 and DW3 are associated with the Sjögren syndrome in patients with primary disease. However, no such link has been noted in patients with the Sjögren syndrome related to rheumatoid arthritis, suggesting that the latter may be a separate disorder.[96]

Renal Disease and Rheumatology

The Goodpasture syndrome is associated with HLA-DRW2.[97] This specificity is in linkage disequilibrium with B7. Multiple sclerosis is similarly associated. Of interest, both conditions tend to have periods of relapse and remission and may be associated with infections or other environmental events. Finally, IgA glomerulonephritis (Berger disease) does not have this or any other HLA association.[98]

Conclusion

Rheumatologic diseases result from a complex interaction between host and environment, and physicians will be successful in treating these disorders only when they learn how to modify one, the other or both. We are beginning to recognize certain genetic contributions; it is hoped that this will lead to increased understanding of the host response and the nature of the causes involved. If progress in research continues at its present rate, our initial optimism will not be ill founded.

REFERENCES

1. Wright V, Moll JMH: Seronegative Polyarthritis. Amsterdam, North-Holland Publishing Company, 1976
2. Ansell BM, Bywaters EGL: Juvenile chronic polyarthritis, *In* Scott JT (Ed): Copeman's Textbook of the Rheumatic Diseases. Edinburgh, Churchill Livingston, 1978, pp 365-388
3. Kellgren JH: Heberden Oration, 1963—The epidemiology of rheumatic diseases. Ann Rheum Dis 23:109-122, 1964
4. Moll JMH, Wright V: Familial occurrence of psoriatic arthritis. Ann Rheum Dis 32:181-201, 1973
5. Emery AEH, Lawrence JS: Genetics of ankylosing spondylitis. J Med Genetics 4:239-244, 1967
6. Gasser DL, Silvers WK: Genetic control of the immune response in mice—An association between H-2 type and reaction to H-Y. J Immunology 106:875-876, 1971
7. Christian CL: Clues from genetic and epidemiologic studies. Arthritis Rheum 21:S130-138, 1978
8. Steinberg AD, Klassen LW, Raveche ES, et al: Study of the multiple factors in the pathogenesis of autoimmunity in New Zealand mice. Arthritis Rheum 21:S190-201, 1978
9. Reinertsen JL, Klippel JH, Johnson AH: B-lymphocyte alloantigens associated with systemic lupus erythematosus. N Engl J Med 299:515-518, 1978
10. Agnell V: Association of systemic lupus erythematosus and SLE-like syndromes with hereditary and acquired complement deficiency states. Arthritis Rheum 21:S146-152, 1978
11. Woolsey RL: Procaineamide lupus and antinuclear antibodies: Role of acetylator phenotype. N Engl J Med 298:1157-1159, 1978
12. Bodmer WF (Ed): The HLA system. Br Med Bull 34:213-316, 1978
13. McDevitt HO, Engleman EG: Association between genes in the major histocompatibility complex and disease susceptibility. Arthritis Rheum 20:S9-20, 1977
14. Eddleston AL, Williams R: HLA and liver disease. Br Med Bull 34:295-300, 1978
15. Cudworth AG, Festenstein H: HLA genetic heterogeneity in diabetes mellitus. Br Med Bull 34:285-289, 1978
16. Calin A, Fries JF: Ankylosing spondylitis: Discussions in Patient Management. Garden City, New York, Medical Examination Publishing Company, Inc, 1978
17. Lawrence JS: Prevalence of rheumatoid arthritis. Ann Rheum Dis 20:11-17, 1961
18. Lawrence JS, Wood PHN: Genetics of rheumatoid arthritis, *In* Duthie JJR, Alexander WRM (Eds): Rheumatic Diseases. Edinburgh, University Press, 1968, pp 19-28
19. Stastny P: HLA-D typing in rheumatoid arthritis. Arthritis Rheum 20:S545-551, 1977
20. McMichael AJ, Sasazuki R, McDevitt H, et al: Increased frequency of HLA CW3 & HLA DW4 in rheumatoid arthritis. Arthritis Rheum 20:1037-1042, 1977
21. Stastny P: Association of the B-cell alloantigen DRW4 with rheumatoid arthritis. N Engl J Med 298:869-871, 1978
22. Panayi GS, Wooley P, Batchelor JR: Genetic basis of rheumatoid disease: HLA antigens, disease manifestations and toxic reactions to drugs. Br Med J 2:1326-1328, 1978
23. Mielants H, Veys EM: A study of the hematological side effects of levamisole in rheumatoid arthritis with recommendations. J Rheum 5 (Suppl):77-83, 1978
24. Brewerton DA, Caffrey M, Hart FD, et al: Ankylosing spondylitis and HL-A 27. Lancet 1:904-905 1973
25. Schlosstein L, Terasaki PI, Bluestone R, et al: High association of an HL-A antigen, W27, with ankylosing spondylitis. N Engl J Med 288:704-705, 1973
26. Bodmer WF: Histocompatibility testing international. Nature 256:696-698, 1975
27. Brewerton DA, Caffrey M, Nicholls A, et al: The histocompatibility antigen HL-A 27 and its relation to disease. J Rheum 1:249-253, 1974
28. Sonozaki H, Seki H, Chang S, et al: Human lymphocyte antigen, HLA 27 in Japanese patients with ankylosing spondylitis. Tissue Antigens 5:131-136, 1975
29. Good AE, Kawanish H, Schultz JS: HLA B27 in Blacks with ankylosing spondylitis or Reiter's disease. N Engl J Med 294:166, 1976
30. Gofton JP, Chalmers A, Price GE, et al: HLA B27 and ankylosing spondylitis in British Columbia Indians. J Rheum 2: 314-318, 1975
31. Ryder LP, Svejgaard A: Associations between HLA and disease—Report from the HLA and Disease Registry of Copenhagen. Copenhagen, Published by authors, 1976
32. Calin A, Bennett PH, Jupiter J, et al: HLA B27 and sacroiliitis in Pima Indians—Association in males only. J Rheum 4: 44-48, 1977
33. Lassus A: Circinate erosive balanitis. Ann Rheum Dis 34 (Suppl):54, 1975
34. Brewerton DA, Albert E: Rheumatology, *In* Dausset J, Svejgaard A (Eds): HLA and Disease. Copenhagen, Munksgaard, 1977, pp 94-107
35. Arnett FC, Schacter BZ, Hochberg MC, et al: Homozygosity for HLA B27. Arthritis Rheum 20:797-804, 1977
36. Calin A, Fries JF: Striking prevalence of ankylosing spondylitis in 'healthy' W27 positive males and females—A controlled study. N Engl J Med 293:835-839, 1975
37. Cohen LM, Mittal KK, Schmid FR, et al: Increased risk for spondylitis stigmata in apparently healthy HLA W27 men. Ann Intern Med 84:1-7, 1976
38. Truog P, Steiger U, Contu L, et al: Ankylosing spondylitis: A population and family study using HLA serology and MLR. Histocompatibility Testing 788-796, 1975
39. Kidd KK, Bernoco D, Carbonara AD, et al: Genetic analysis of HLA-associated diseases: The 'illness-susceptible' gene frequency and sex ratio in ankylosing spondylitis, *In* Dauset J, Svejgaard A (Eds): HLA and Disease. Copenhagen, Munksgaard, 1977, pp 72-80

40. HLA-B27 and risk of ankylosing spondylitis (Editorial). Br Med J 2:650-651, 1978

41. Hill HFH, Hill AGS, Bodmer JG: Clinical diagnosis of ankylosing spondylitis in women and relation to presence of HLA B27. Ann Rheum Dis 35:267-270, 1976

42. Resnick D, Dwosh IL, Goergen TG, et al: Clinical and radiographic abnormalities in ankylosing spondylitis: A comparison of men and women. Radiology 119:293-297, 1976

43. Braun WE, Dejelo CL, Clough JD, et al: No association of known DR antigens with ankylosing spondylitis. N Engl J Med 298:744-745, 1978

44. Arnason A, Thorsteinsson J, Sigurbergsson L: Ankylosing spondylitis, HLA-B27 and Bf. Lancet 1:339-340, 1978

45. Migone N, Malavasi F, Boschis D, et al: Bf polymorphism and ankylosing spondylitis. Lancet 2:163, 1978

46. Terasaki P, Mickey MR: HLA haplotypes of 32 diseases. Transpl Rev 22:105, 1975

47. Arnett C, Schacter Z, Hochberg MC, et al: HLA A28 in patients with B27-associated rheumatic diseases. Arthritis Rheum 20:106, 1976

48. Calin A, Porta J, Payne R: HLA-A28 in B27 positive controls and patients with ankylosing spondylitis. Arthritis Rheum 20:1428, 1977

49. Kozin F, Duquesnoy R, Rodey GE, et al: High prevalence of HLA-Cw1 and Cw2 antigens in spondylarthritis. Arthritis Rheum 21:889-895, 1978

50. Arnett FC, Hochberg MC, Bias WB: HLA-C locus antigens in HLA-B27 associated arthritis. Arthritis Rheum 21:885-888, 1978

51. Arnett FC, Schacter BZ, Hochberg MC, et al: HLA-B27 cross-reactive antigens in B27-negative Reiter's syndrome, abstracted. Arthritis Rheum 20:106, 1977

52. McDevitt HO, Bodmer WF: HL-A immune response genes and disease. Lancet 1:1269, 1974

53. Grumet FC, Payne RO, Konishi J, et al: HLA antigens in Japanese patients with Graves' disease. Tissue Antigens 6:347, 1975

54. Ebringer RW, Cawdell DR, Cowling P, et al: Sequential studies in ankylosing spondylitis: Association of Klebsiella pneumoniae with active disease. Ann Rheum Dis 37:146-151, 1978

55. Seager K, Bashir HV, Geczy: Evidence for a specific B27-associated cell surface marker on lymphocytes of patients with ankylosing spondylitis. Nature 277:68-70, 1979

56. Corrigal V, Panayi GS, Unger A, et al: Detection of immune complexes in serum of patients with ankylosing spondylitis. Ann Rheum Dis 37:159-163, 1978

57. Geddes DM, Webley M, Brewerton DA, et al: α1-Antitrypsin phenotypes in fibrosing alveolitis and rheumatoid arthritis. Lancet 2:1049-1050, 1977

58. Webley M, Ward DM, Brewerton DA: The α1 antitrpysin phenotype in acute anterior uveitis. Read before Heberden Society, London, Nov 1978

59. Eastmond CJ, Woodrow JC: Discordance for ankylosing spondylitis in monozygotic twins. Ann Rheum Dis 36:360-364, 1977

60. Brewerton DA, Warren RE: Klebsiella pneumoniae. Ann Rheum Dis 37:298, 1978

61. Eastmond CJ, Cooke EM, Wright V: Klebsiella pneumoniae. Ann Rheum Dis 37:298-299, 1978

62. Calin A: Reiter's Syndrome. Med Clin North Am 61:365-376, 1977

63. Keat AC, Maini RN, Nkwazi GC, et al: Role of chlamydia trachomatis and HLA B27 in sexually acquired reactive arthritis. Br Med J 1:605, 1978

64. Ford DK: The etiology of non-gonococcal urethritis and Reiter's syndrome. Excerpta Medica International Congress Series 165:227-229, 1969

65. Csonka GW: Recurrent attacks in Reiter's disease. Arthritis Rheum 3:164, 1960

66. Laird SM: Figures and fancies. Br J Vener Dis 34:137, 1958

67. Schachter J, Barnes HG, Jones JP, et al: Isolation of bedsoniae from joints of patients with Reiter's syndrome. Proceedings of the Society for Experimental Biology and Medicine, 122:283, 1966

68. Keat AC, Thomas BJ, Taylor-Robinson D, et al: IgG antibodies to chlamydia trachomatis in sexually acquired reactive arthritis. Read before Heberden Society, Nov 1978

69. Calin A, Fries JF: An 'experimental' epidemic of Reiter's syndrome revisited—Follow-up evidence on genetic and environmental factors. Ann Intern Med 84:564-566, 1976

70. Hakansson U, Eitrem R, Low B, et al: HLA-antigen B27 in cases with joint affections in an outbreak of salmonellosis. Scand J Infect Dis 8:245-248, 1976

71. Vartiainen J Hurri L: Arthritis due to salmonella typhimurium. Acta Medica Scandinavica 175:771-776, 1964

72. Ahvonen P, Sievers K, Aho K: Arthritis associated with Yersinia enterocolitica infection. Acta Rheum Scand 15:232-253, 1969

73. Aho K, Ahvonen P, Lassus A, et al: HL-A 27 in reactive arthritis: a study of Yersinia arthritis and Reiter's disease. Arthritis Rheum 17:521-526, 1974

74. Calin A, Kaslow R, Simon D, et al: Reiter's syndrome and the seroepidemiology of Shigella. Ann Rheum Dis 38:190, 1979

75. Good AE, Schultz JS: Reiter's syndrome following Shigella flexneri 2a. Arthritis Rheum 20:100-104, 1977

76. Urman JD, Zurier RB, Rothfield NF: Reiter's syndrome associated with campylobacter fetus infection. Ann Intern Med 86:444-445, 1977

77. Berden JHM, Muytjens HL, Putte LBA: Reactive arthritis associated with campylobacter jejuni enteritis. Br Med J 1:380-381, 1979

78. McClusky OE, Lordon RE, Arnett FC: HLA 27 in Reiter's syndrome and psoriatic arthritis: A genetic factor in disease susceptibility and expression. J Rheum 1:263, 1974

79. Calin A, Fox R, Gerber DJ, et al: The natural history of Reiter's syndrome. Arthritis Rheum 21:548-549, 1978

80. Gottlieb M, Calin A, Gale RP: Discordance for psoriatic arthropathy in phenotypically-identical (monozygotic) twins. Arthritis Rheum 22:805-806, 1979

81. White SH, Newcomer VD, Mickey MR, et al: Disturbance of HL-A antigen frequency in psoriasis. N Engl J Med 287:740-743, 1972

82. Espinoza LR Vasey FB, Oh JH et al: Association between HLA-BW38 and peripheral psoriatic arthritis. Arthritis Rheum 21:72-75, 1978

83. Phair JP: Defects in host defense mechanisms that predispose to infection. Clin Rheum Dis 4:3-13, 1978

84. Leirisalo M, Tiilikainen A, Laitinen O: HLA phenotypes in rheumatic fever and yersinia arthritis, abstracted. First International Symposium on HLA & Disease, Paris. Jun 23-25, 1976

85. Greenberg LJ, Gray ED, Yunis EJ: Association of HL-A 5 and immune responsiveness in vitro to streptococcal antigens. J Exp Med 141:935, 1975

86. Robitaille C, Cockburn C, James DCO, et al: HLA frequencies in less common arthropathies. Ann Rheum Dis 35:271-273, 1976

87. Mirise RT, Kitridou RC: Arthritis and hepatitis. West J Med 130:12-17, 1979

88. Inman RD: Immunologic sex differences and the female predominance in systemic lupus erythematosus. Arthritis Rheum 21:849-852, 1978

89. Sany J, Seignalet J, Serre H, et al: HLA in polymyalgia rheumatica, abstracted. First International Symposium on HLA and Disease, Paris, Jun 23-25, 1976

90. Shapiro RF, Utsinger PD, Wiesner KB, et al: HLA B27 and modified bone formation. Lancet 1:230-231, 1976

91. Rosenthal M, Bahous I, Muller W: HL-A B27 and modified bone formation. Lancet 1:543, 1976

92. Singal DP, de Bosset P, Gordon DA: Comparison of osteitis condensans ilii and ankylosing spondylitis in female patients: Clinical, raiological and HLA typing characteristics (Abstract), *In* Dausset J, Svejgaard A: Inserm HLA and Disease. Paris, Inserm, 1976, p 52

93. Madkour M, Kudwah A: Behcet's disease. Br Med J 2: 1786, 1978

94. Ohno S, Aoki K, Sugiura S, Nakayama E, et al: HL-A5 and Behcet's disease. Lancet 2:1383, 1973

95. Chamberlain MA: Behcet's disease. Ann Rheum Dis 34: 53, 1975

96. Chused TM, Kassan SS, Moutsopoulos HM, et al: Sjögren's syndrome associated with the lymphocyte-defined antigen HLA-DW3. Arthritis Rheum 20:112, 1977

97. Rees AJ, Peters DK, Compston DAS, et al: Strong association between HLA-DRW2 and antibody-mediated Goodpasture's syndrome. Lancet 1:966-968, 1978

98. Nagy J, Hámori A, Ambrus M, et al: More on IgA glomerulonephritis and HLA antigens (Correspondence). N Engl J Med 300:92, Jan 11, 1979

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Factitious Disease in Pediatrics

MARTIN STEIN, MD:* *Children who present with microscopic or gross hematuria require prompt diagnostic evaluation in order to determine the cause of the disorder. Pediatricians often encounter young patients with painless hematuria; careful microscopic examination of the urine for red blood cell casts and determination of the protein content of the urine may suggest a diagnosis of glomerulonephritis. In the absence of red blood cell casts, suspected diagnoses include urinary tract infection, obstructive uropathy, renal trauma, coagulopathy and renal tumor.*

Children present less commonly with painful hematuria. The presence of pain suggests obstruction or inflammation, and diagnostic considerations may differ from those used for children with painless hematuria. The patient to be presented illustrates the clinical dilemma of a child who has experienced recurrent episodes of painful hematuria that have evaded diagnostic classification.

DEBORAH RUFNER, MD:† A 10-year-old boy presented with a history of recurrent painful hematuria. When he was 4 years old, he had experienced dysuria associated with gross hematuria. At that time, physicial examination showed no unusual findings. The blood pressure was normal. Analysis of urine showed numerous red blood cells; protein was not found and urine cultures were negative. Tests for blood urea nitrogen and serum creatinine gave normal values. Urologic evaluation, which included an excretory urogram, voiding cystourethrogram and cystoscopy, showed no abnormalities. Over the next six years, he experienced eight episodes of painful gross hematuria. Fever was not associated with any episode and each lasted less than 24 hours. When he was 6 years old, a second evaluation was made, which included contrast studies and cystoscopy; results of these studies were also negative. Numerous analyses of urine between these episodes gave normal findings. After another episode when he was 10 years of age, he was referred to the pediatric department. At that time, excretory urogram, voiding cystourethrogram, and cystoscopy were all again normal.

There was nothing unusual in his history. There was no history of trauma, masturbation or urological surgical procedures. A drug history showed nothing exceptional. His diet was appropriate for a school-age child, and excessive intake of calcium, vitamin D or high oxalate foods was

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not noted. His family history showed no renal disease, urolithiasis or hearing problems.

There were no significant findings on physical examination. Blood pressure was 100/60 mm of mercury. Height and weight were at the 50th percentile for age. An analysis of urine showed no abnormalities. Tests showed normal values for blood urea nitrogen, serum creatinine, calcium, phosphorus, sodium, potassium, chloride, bicarbonate and uric acid. Several urine cultures for bacteria and for Mycobacterum tuberculosis gave negatives results, as did a tuberculin skin test.

DR. STEIN: *At this time, let us entertain a differential diagnosis of hematuria in children, but first let us see if there are any questions. For instance, it would assist us to know if this patient ever had an episode of painless hematuria. In addition, did you characterize the timing of the pain with reference to his urinary stream, and did he experience any abnormality of his urinary stream?*

DR. RUFNER: Pain was a constant feature, and it occurred throughout urination. Urination was free from hesitancy, urgency, intermittency and deviation of the direction of urine flow. We observed a normal urinary stream on several occasions.

CHARLES INMAN, MD:* Did you localize the region of the pain?

DR. RUFNER: It was penile pain. There were no abdominal symptoms.

JOHN WELSH, MD:† Was there anything unusual in this child's development? Did he undertake any peculiar activities?

DR. RUFNER: His mother reported that his development and activities were not unusual.

PHYSICIAN IN AUDIENCE: Did he experience urethral pain when he was not urinating?

DR. RUFNER: No.

DR. STEIN: Banana-seat *hematuria has been described in children who ride bicycles with long hard seats. Presumably they experience a perineal contusion that leads to hematuria. Was he an avid bicycle rider?*

DR. RUFNER: No, not any more than most children.

PHYSICIAN IN AUDIENCE: Did you inquire about a family history of bleeding disorders?

DR. RUFNER: There was no family history of bleeding diathesis. Furthermore, prothrombin time, partial thromboplastin time and platelet count were normal.

MEDICAL STUDENT: Are there any drugs that are associated with blood in the urine?

DR. STEIN: *Some drugs are associated with hematuria, others with hemoglobinuria and still others with a red discoloration not associated with heme pigment. Frequently prescribed drugs that have been associated with hematuria include penicillins (including methicillin and ampicillin), sulfonamides, kanamycin, amphotericin, acetylsalicylic acid, corticosteroids, cyclophosphamide, indomethacin, phenylbutazone, probenecid, heparin and warfarin.*[1] *Hemoglobinuria, which is defined as the presence of dissolved hemoglobin in the urine, may be secondary to a drug-induced hemolysis. Drugs prescribed by pediatricians that may cause a red discoloration of the urine not associated with hemoglobin include nitrofurans, phenazopyridine, phenothiazines, phenytoin, rifampin, sulfonamides, deferoxamine, methyldopa, phenacetin and phenolsulfonphthalein* (EXLAX).[2] *This child's drug history was negative. In addition, the red discoloration of urine caused by drugs is not associated with pain.*

The differential diagnosis developed by the participants in the audience is shown in Table 1. In the discussion, the universal presence of pain was emphasized as well as the absence of red blood cell casts and the substantial workup, which ruled out glomerulonephritis. Several common causes of gross hematuria in children are typically painless, including hydronephrosis with or without trauma, polycystic disease of kidney, sickle cell trait and disease, SC *hemoglobinopathy, Wilms tumor, familial and benign hematuria.*[3] *Although the localization of the pain on urination was penile and therefore suggested lower urinary tract pathology, an extraglomerular upper-tract bleeding from various causes with subsequent clot formation was considered possible.*

The probable diagnosis, or at least that favored by most of the participants, was renal calculus, which may cause episodic findings and may evade

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clinical detection. The subsequent clinical course of this patient was elucidated by Dr. Stapleton.

F. BRUDER STAPLETON, MD:* Renal calculi are uncommon in children. The incidence of urolithiasis ranges from 1 in 3,000 to 1 in 7,600 pediatric patients admitted to hospital. There is a predilection for boys, particularly before the age of 2 years. Unlike the situation in some parts of the world, there are no endemic areas for renal calculi in the United States. In children, stones occur most commonly in the first few years of life, probably reflecting the association of calculi with obstructive uropathy. Calculi are bilateral in 33 percent of cases.[3] Calculi are uncommon in black children.

In a review of renal calculi in children, Piel and Roof reviewed 445 cases,[4] in 33 percent of which the calculi were considered to be idiopathic. This finding differs significantly from the 65 percent incidence of idiopathic renal calculi in adults. Urinary tract infection, with or without obstruction, is thought to account for 58 percent of renal calculi, but there is controversy over whether infection is a primary initiating factor in or a sequel to stone formation.[5] Most calculi are associated with urinary tract infections with proteus species. Proteus and other urea-splitting bacteria produce an alkaline urine, and stone growth in alkaline urine may be dramatic. When immobilization and its attendant hypercalciuria accompany a proteus infection, a very hospitable environment is prepared for the development of a urinary tract calculus. Children with meningomyelocele frequently have urolithiasis, presumably as a result of this association. Other causes of urolithiasis in children are uncommon because virtually all the calculi reported are idiopathic or are associated with infection and obstructive uropathy.

Uric acid stones account for 2 percent of renal calculi; oxalate stones comprise 1 percent; and cystine stones are responsible for 4 percent of urolithiasis in children. Idiopathic hypercalciuria accounts for 2 percent of pediatric renal calculi and hypercalciuria associated with immobilization produces another 4 percent.[6] Hypercalciuria associated with distal renal tubular acidosis produces 1.5 percent of renal stones. Hyperparathyroidism is found in fewer than 1 percent of patients with renal calculi.[4-7]

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Certain children form renal stones because they excrete excessive quantities of crystalloids in their urine. Hypercalciuria may or may not be associated with hypercalcemia. Causes of hypercalcemia include immobilization, vitamin D excess, hyperparathyroidism, hypothyroidism and hyperthyroidism, hypophosphatasia, sarcoidosis and malignancies. Hypercalciuria may be idiopathic or secondary to acidosis or corticosteroid therapy. Idiopathic hypercalciuria may result either from increased intestinal absorption of calcium or from a renal tubular defect in calcium reabsorption. Normal calcium excretion is less than 5 mg per kg of body weight per 24 hours or a urinary calcium/creatinine ratio of less than 0.2. Moore and associates recently reviewed the subject of idiopathic hypercalciuria in children.[6]

Calcium oxalate calculi occur in primary oxalosis. Type 1 oxalosis is due to an absence of α-ketoglutarate: glyoxylate carboligase. Urinary excretion of oxalate, glyoxylic acid and glycolic acid are increased. Type 2 oxalosis is due to a deficiency of D-glyceric dehydrogenase, and urinary excretion of L-glyceric acid is increased. Increased quantities of oxalate may appear in the urine in the presence of large intakes of ascorbic acid or oxalate-rich foods such as rhubarb and spinach as well as in inflammatory bowel disease. Normal oxalate excretion is less than 50 mg per 1.73 square meters of body surface per 24 hours. Cystine stones occur in patients with cystinuria. Normal excretion of cystine is less than 20 mg per 1.73 square meters of body surface per 24 hours. Uric acid stones may occur with or without hyperuricemia. Primary hyperuricemia is unusual in children, but secondary hyperuricemia may result from myeloproliferative disorders, from decreased renal excretion in renal disease or from acidotic states. Normal values for uric acid excretion vary with age and are higher than adult values until late childhood.[8]

Signs and symptoms associated with renal calculi in children include pyuria, hematuria, abdominal distension, urinary retention, dysuria, abdominal pain and renal colic. It appears that pain accompanies stones less frequently in children than in adults. Other symptoms include fever, anorexia and enuresis.

When evaluating a child with suspected urolithiasis, the history is extremely important. Cogent information includes a family history of renal stones, diet, medication (including vitamins) and a history of infections or urologic symptoms. It

is also important to note whether growth has been normal. Laboratory evaluation should include assessment of renal function (creatinine clearance) and the serum concentrations of electrolytes, protein, calcium, phosphorus, magnesium and uric acid, as well as a urine culture. Measurements of the urinary excretion of calcium, uric acid, oxalate, cystine and amino acids may be necessary. Xanthine excretion should be measured if hypouricemia is present or if the patient is being treated with allopurinol. Roentgenograms of the abdomen may show opaque calculi or nephrocalcinosis. The excretory urogram is essential to show radiolucent calculi. If calculi are retrieved, they should be analyzed chemically.

In the case presented, neither history, laboratory examination nor radiologic studies defined the cause of the problem. No crystals were ever found on analyses of the urine. The urine pH was 5.0. Serum bicarbonate was 24 mEq per liter; other serum values were calcium 10 mg per dl, phosphorus 3.8 mg per dl, magnesium 2.0 mg per dl, uric acid 4.0 mg per dl and creatinine 0.5 mg per dl. Values for the urinary amino acids including cystine were normal. Urinary excretion of calcium was 117 mg per 24 hours (3 mg per kg of body weight); uric acid excretion was 350 mg per 24 hours (12 mg per kg of body weight). and oxalate excretion was 20 mg per 24 hours. The tubular reabsorption of phosphate was 87 percent. Roentgenograms showed normal bones. Nevertheless, we suspected urolithiasis. Subsequent to this evaluation, dysuria again developed in this boy; moreover, his mother witnessed the passage of a stone from his penis. We submitted the stone for crystallographic analysis; its mineral content was found to be 100 percent quartz. Somehow, rocks had traversed the urethra. Unfortunately, I had only a single visit with the family before they were transferred from the area. I recommended that the family seek psychological counseling at their new residence. The child suggested that his sister may have placed the rocks in the container.

The story is not unprecedented. Sneed and Bell[9] reported a 10-year-old child who repeatedly passed quartz calculi; and, on one occasion, fragments of an insect were found in his urine. They reported that the boy's mother had actually palpated a calculus in the urethra. These authors emphasize that factitious calculi may be a manifestation of the Munchausen syndrome.

It is possible that the patient really did have intermittent calculi and that he was merely attempting to assist in making the diagnosis. However, there was a clinical clue that the stones were factitious. Urolithiasis is usually accompanied by crystalluria, and this patient never had crystals in the urine.

DR. STEIN: *The available data point to a diagnosis of factitious urolithiasis. This school-age child appeared to be experiencing repeated episodes of painful urination associated with gross and microscopic hematuria as a result of inserting foreign objects into his urethra. A detailed developmental history may have shown areas of disharmony in parent-child relationships or in peer and school activities.*

Functional illness requires thorough diagnostic evaluation just as do clearly defined organic problems. A diagnosis of psychosomatic disease is not a diagnosis of exclusion. It requires positive findings of emotional stress in the child's environment that are consistent with barriers to age-specific developmental tasks. Pediatricians, who view children within a developmental perspective, are uniquely equipped to engage the school-age child and his parents in seeking a developmental data base.

In a 10-year-old patient with recurrent painful hematuria, a developmental history should emphasize the following areas: function in school (achievement, peer relations, activities), sleep disturbances (enuresis, nightmares, night terrors or somnambulism), development of superego function (guilt, shame or blame in family or peer activities), problems of elimination (vomiting, constipation, abdominal pain and enuresis), past and present masturbation (frequency in patient, parental attitudes and reactions to) and the effect of repeated urologic procedures on the child's self-image and behavior. This pattern of information gathering could provide important clues to the etiology of factitious urolithiasis.

RESIDENT IN AUDIENCE: The child who inserts a foreign body in an orfice can be a diagnostic enigma when the presenting complaint distracts the physician from the real problem. Recently, a 2-year-old boy was brought to the Primary Care Clinic by his mother who was very concerned about a peculiar, persistent and noxious odor emanating from this child. The toddler had previously been healthy and the initial physical ex-

amination showed normal findings; the reported odor was not documented in the clinic. When the child returned to the office a week later with the same complaint, examination of the nasal cavity showed a thick, green, malodorous discharge from one naris. Following the removal of a small piece of cotton material from the nasal cavity, the odor resolved. Upon further questioning, the mother stated that the child had been observed inserting foreign objects into his nose on several occasions.

DR. STEIN: *These are dramatic examples of body exploration and experimentation undertaken by every toddler. In this developmental stage, the 2-year-old is exploring his or her environment, and there is frequent hand-to-mouth activity. One type of excess of this sort is pica. We have recently seen a toddler with acute abdominal pain, vomiting and diarrhea.*

Figure 1.—Kidney, ureter and bladder roentgenogram of the patient described in text, showing multiple calcific densities in a distribution that matched the position of the colon (arrows).

Figure 2.—Living snails (Helix aspersa), radiographed in a water bath.

Figure 3.—Crushed snail shells radiographed in a water bath. (Note similarity to the abdominal densities in Figure 1.)

DAVID K. EDWARDS, MD:* A roentgenogram of the abdomen (Figure 1) showed vague radiopaque densities that were not present on a subsequent kidney, ureter and bladder film. The mother initially denied pica but subsequently recalled that the child occasionally ate garden snails. We were uncertain about the radiographic appearance of intra-abdominal snail shells. To resolve our uncertainty, I gathered local snails (Helix aspersa) from my own garden and radiographed them in a water bath (Figure 2). Empty shells, which had been crushed to simulate what would happen if they were chewed, were radiographed in a water bath; they presented an appearance (Figure 3) very similar to the calcific densities noted on the initial film of the child's abdomen. The resident staff maintained that this child represented a case of "escargot pica of childhood."

DR. STEIN: *Other orifices than the mouth are occasionally used by young children as receptacles for objects of play. A 5-year-old girl was recently evaluated in the Primary Care Clinic for a six-month history of persistent vaginal discharge. A course of antibiotics and frequent sitz baths were not beneficial. The vaginal mucosa was erythematous and a minimal grey discharge was observed. Visualization of the vaginal cavity with an otoscope showed a black object deep in the vaginal vault which, surprisingly, was not palpated during rectoabdominal examination. The foreign body could not be removed using a speculum and a topical spray anesthetic. While waiting for a scheduled pelvic examination under general anes-*

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TABLE 1.—*Differential Diagnosis of Painful Hematuria in a School-Age Child*

Calculi
Trauma: abdominal, perineal or penile
Foreign body: bladder or urethral
Infection: bacterial, Mycobacterium tuberculosis or viral
Coagulation disorders
Tumor
Hemangioma: bladder or urethral
Meatal stenosis with ulcer

thesia, urethral suppositories of nitrofurantoin (Furadantin) were prescribed to be inserted in the vagina twice a day. The patient's mother phoned within three days to report that a 1-cm steel bolt was spontaneously passed from the vaginal opening along with the slurry created by the suppository.

This case was similar to that of the child with factitious urolithiasis in that she was an older child who selected a genital orifice as the receptacle for a foreign body. Her family was medically oriented and made a conscious effort to use explicit terms for the genitals when speaking even to the youngest child. In this context, exploratory genital play may reflect inquisitiveness and unique family influences in this bright preschool child. Her subsequent emotional and physical development has been normal.

WILLIAM NYHAN, MD, PHD:* It is important to emphasize the diagnostic difficulties imposed by the pediatric patient with factitious disease. As pediatricians, our customary patterns of thought do not readily lead us to suspect that a child may be producing the problem with which he presents. Oh, we do readily make the diagnosis in a child with a foreign body in the vagina or a child with a foreign body in the nose, who presents with discharge or a terrible odor. These examples are encountered relatively commonly in practice. A child with a long history of painful hematuria is something else again. I am impressed with the fact that possibility of a foreign body was considered in the differential diagnosis developed in Table 1. On the other hand, this conference is designed to teach problem solving. Those physicians who had seen the patient appropriately considered that he had a urinary-tract calculus until contrary proof was established. Similarly, the intra-abdominal densities observed in the patient with an unusual taste for escargot provided a confusing diagnostic challenge. Awareness of the problem of factitious disease with its wide spectrum of presentation should heighten our indices of diagnostic suspicion.

*Professor and Chairman, Department of Pediatrics.

REFERENCES

1. Lieberman E: Clinical Pediatric Nephrology. Philadelphia, JB Lippincott Co, 1976, pp 13-14
2. Knoben JE, Anderson PO, Watanabe AS: Handbook of Clinical Drug Data. Hamilton, IL, Drug Intelligence Publication, 1978.
3. West CD: Asymptomatic hematuria and proteinuria in children: Causes and appropriate diagnostic studies. J Pediatr 89: 173-182, 1976
4. Piel CF, Roof BS: Renal calculi, *In* Rubin MT, Barrett TM (Eds): Pediatric Nephrology. Baltimore, Williams & Wilkins Co, 1975
5. Mathieu H: Urinary lithiasis, *In* Royer P, Habib R, Mathieu H, et al (Eds): Pediatric Nephrology. Philadelphia, WB Saunders, 1974
6. Moore ES, Coe FL, McMann BJ, et al: Idiopathic hypercalciuria in children: Prevalence and metabolic characteristics. J Pediatr 92:906-910, 1978
7. Wenzl JE, Burke EC, Stickler GB, et al: Nephrolithiasis and nephrocalcinosis in children. Pediatrics 41:57-61, 1968
8. Stapleton FB, Linshaw MA, Hassenein K, et al: Uric acid excretion in healthy children. J Pediatr 92:911-914, 1978
9. Sneed RC, Bell RF: The Dauphin of Munchausen: Factitious passage of renal stones in a child. Pediatrics 58:127-130, 1976

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Asbestos-Related Lung Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *This Grand Rounds concerns a subject of considerable interest in the fields of environmental and occupational health. Dr. Jeffrey A. Golden will discuss asbestos-related lung disease.*

DR. GOLDEN:† Asbestos has been known since ancient times, when it was called the "funeral dress of kings" because it was used to wrap the bodies of kings before they were placed on funeral pyres.

Exposure to asbestos can result in various thoracic manifestations: hyaline pleural plaques, pleural calcifications, benign pleural effusions, pulmonary fibrosis, malignant mesothelioma and bronchogenic carcinoma. Of these, only pulmonary fibrosis or asbestosis is the true pneumoconiosis associated with asbestos inhalation. In the middle of the 19th century, Zenker coined the term pneumoconiosis in reference to fibrotic diseases of the lung that result from inhalation of inert particles or fibers.[1] Tumors and various pleural diseases do not fall under this category.

There has been a tremendous delay in recognizing the potential for disease resulting from inhalation of asbestos fibers. Two reasons for this delay are that the various diseases due to asbestos inhalation do not appear until many years after initial contact with the fibers and that there has been a lack of clear communication between epidemiologists and the clinicians about the potential of asbestos inhalation. To bridge the gap between clinicians and epidemiologists, I will review the epidemiologic data that relate to asbestos exposure.

Asbestos fibers are actually a collection of different silicates of iron and magnesium that share two common characteristics. They are fibers —that is, their lengths are at least three times greater than their diameters—and they have tremendous resistance to heat. The various fibers differ in their chemical and physical properties. For example, the chrysotile fiber is very long and wavy, and is widely used in textiles in which insulation is important. Other fibers, such as crocidolite, are very short and acid resistant, making them ideal for marine insulation. Some asbestos products, for example, cements, contain both chrysotile and crocidolite.

The single most important point in this clinical discussion is that taking a thorough occupational history in mandatory. There are direct and indirect exposures to asbestos. Direct exposure includes three types of encounters: (1) the production of the fiber itself involving its mining and milling, (2) the manufacture of products that are required for insulation such as textiles, cements, roofing

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and flooring materials and (3) the application of these materials or the demolition of structures containing asbestos products. Any manipulation that disperses these fibers into the air, such as cutting through insulation board, places the health of the workers involved in jeopardy. If a patient is a solderer, one must ask where he or she has been working. For example, was he employed at a shipyard soldering in a compartment of a submarine in which someone else was cutting asbestos board? Such facts are of great importance in evaluating a patient's respiratory disorder.

Indirect exposures include neighborhood and household contacts. In Finland, for example, there is an increased incidence of adult-acquired mesothelioma in persons who as children lived near asbestos mines. In fact, investigators have shown that asbestos fibers can be measured in the air at some distance from these mines.[2] Household contact can occur by exposure to asbestos fibers from overalls worn by a worker who lives in the same house. Among persons indirectly exposed, there is an 8 percent incidence of radiographically detectable plaques indicative of asbestos exposure.[3]

Pulmonary disease can result from inhaling asbestos fibers. The distance that a compact particle penetrates the lung depends on its falling speed, a factor critically related to its aerodynamic diameter. For compact particles longer than 5 μ, the nose is an effective filter; whereas for particles shorter than 5 μ there is an increasingly peripheral deposition in the lung. Surprisingly, the peripheral deposition of long fibers such as asbestos is similar to that of compact particles. Where laminar airflow exists, such as in the small respiratory airways, fibers tend to align themselves parallel to the air stream. In fact, the falling speed of fibers relates not to their lengths but to their diameters, which are invariably well under 5 μ.[4] As inhaled asbestos fibers reach the respiratory bronchioles, they first come into contact with the macrophages that normally tend to aggregate in the vicinity of small airways. These macrophages engulf the fibers, coating them with ferritin granules to form what is referred to as asbestos bodies. The presence of these asbestos bodies in the sputum is indicative of asbestos exposure, although not necessarily indicative of any pathologic implication. In fact, other fibers such as fiberglass, cotton and talc similarly become coated with ferritin, forming similar ferruginous bodies.[1]

The first histopathologic entity I will discuss is the pleural plaque. In asymptomatic persons exposed to asbestos, pleural plaques are usually discovered on routine radiographs of the chest. If one is particularly interested in finding such plaques, high kilovoltage techniques should be used, and a patient should be examined radiographically in various oblique positions to detect plaques not evident on single posterior-anterior projections. These plaques often align themselves along rib margins. The genesis of the plaques on the parietal pleura is not clear. It may be that fibers of asbestos migrate to the periphery of the lung and penetrate the visceral pleura; however, no data have been reported to support this hypothesis. It has also been proposed that asbestos fibers spread in a retrograde manner into the pleural lymphatics from hilar lymph nodes, another hypothesis for which there are no data.

A typical pleural plaque is discrete and whitish, and emanates from the parietal pleura. On microscopic examination these plaques are composed of collagen with a minimal cellular component. With light microscopy asbestos fibers are not apparent in these plaques, but on examination with an electron microscope small uncoated fibers can be seen. I am frequently asked about the significance of these pleural plaques. As with the finding of asbestos bodies in sputum, the presence of pleural plaques indicates only exposure to asbestos and does not imply that a mesothelioma, pulmonary fibrosis or bronchial carcinoma will develop.

Let us move to a discussion of pleural calcifications. Diaphragmatic calcifications are pathognomonic for asbestos exposure, especially when such calcifications are bilateral. In contrast to the search for pleural plaques, when one is looking for pleural calcification low kilovoltage techniques should be used. Calcification of a plaque is not dependent on the size of the plaque but appears to be related to the amount of time since the first exposure to asbestos.[3] I must reemphasize that as with pleural plaques, calcifications do not imply that fibrosis or a tendency for mesothelioma, or any other manifestation of disease resulting from asbestos exposure, will develop. It is interesting that one often observes pleural and pericardial calcified plaques incidentally when using more sensitive techniques such as computerized axial tomography (CAT) scans.

A less frequently recognized manifestation of asbestos exposure is benign pleural effusion. Gaensler studied 24 cases of persons exposed

to asbestos in whom pleural effusions developed and showed that often the effusions were associated with mesothelioma and lung carcinoma.[4] He also described a group of 12 subjects who had exudative pleural effusions with pleuritic pain which were not associated with mesotheliomas. As an example, Gaensler presented the case of an asbestos worker in whom severe pain and an exudative pleural effusion developed in the left side of the chest. A subsequent pleural stripping relieved the pain. Several years later the same patient was admitted to hospital five times with pain and effusion on the other side of his chest, but the new effusion resolved spontaneously, leaving him with a slightly thickened pleura. A follow-up of the same patient eight years after the problems first appeared showed no suggestion of a mesothelioma.

This example provokes an important question, what does one do when an asbestos worker presents with a bloody pleural effusion? I suggest that one should follow the case carefully, and, if need be, treat the patient with repeated thoracenteses. Such an effusion is not necessarily a harbinger of mesothelioma. There appears to be an entity of benign exudative pleural effusions associated with asbestos exposure.

The remaining discussion will deal with asbestosis, the pneumoconiosis associated with asbestos exposure. Pneumoconiosis was the first disease recognized as being related to asbestos exposure. In 1924 Cook described the case of a textile worker who died of asbestos pneumoconiosis.[1] As mentioned above, asbestos fibers tend to accumulate in the respiratory bronchioles where macrophages aggregate. The earliest finding in experimental asbestosis in animals is not an interstitial disease, but a small airway disease. It is only later, as in the case of human autopsy or biopsy specimens, that one witnesses the thickening of the alveolar capillary membrane associated with asbestos bodies. The asbestos pneumoconiosis begins peripherally in the lower lobes, unlike silicosis. Only in severe cases does one observe a diffuse spread of the interstitial process. Like any interstitial process, a honeycomb lung may result with the subsequent development of cysts.

The radiographic manifestations can be seen as a continuum, being somewhat dependent on the degree of exposure. Because there is a continuum, a category scale or profusion index has been developed. A zero category includes only minimal lower lobe irregular opacities. Category 1 includes obvious opacities, but not so severe as to obscure the underlying lung markings. Category 2 implies numerous irregular opacities which in part obscure the normal markings. In category 3, an x-ray study will show opacities so numerous as to obscure totally the underlying lung (Figure 1). It should be emphasized that radiographic abnormalities are not specific for asbestosis. Even in category 3, a radiograph will not confirm a diagnosis of asbestosis. Also, the radiographic category does not relate well to the disability caused by asbestosis. There are other radiographic manifestations of asbestosis exposure such as massive fibrotic lesions that in the past were recognized only in persons with coal miner's disease. In fact, progressive massive fibrosis can occur in asbestosis, as well as in coal miner's disease.

A Caplan-like syndrome with necrobiotic nodules can also be seen on x-ray examination of persons who have been exposed to asbestos and

Figure 1.—Radiograph of worker with asbestosis showing irregular densities obscuring underlying lung markings (category 3; see text).

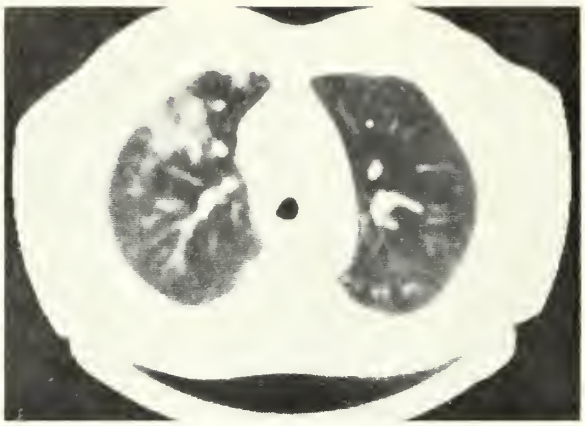

Figure 2.—Computerized axial tomographic (CAT) scan showing changes consistent with interstitial fibrosis in worker with asbestosis with normal anterior-posterior chest film.

who have rheumatoid arthritis. Finally, a single discrete lesion, the asbestoma, has been observed.

One of the major problems in diagnosing asbestosis involves the sensitivity of the radiographic examination. There are examples of severely dyspneic asbestos workers with interstitial disease in whom tests show abnormal pulmonary function but radiographs of the chest are normal. Are there more sensitive types of laboratory examinations? If one carries out a CAT scan in such cases, one may observe findings consistent with interstitial fibrosis (Figure 2). Other tools are being investigated. One is gallium scanning.[5] For instance, persons with silicosis have been found to have dramatically increased pulmonary uptake of gallium, indicating that the abnormality is much greater than that suggested by routine radiographic examination. Therefore, whether one finds radiographic evidence of asbestosis may depend on which tool is used. On the other hand, there are persons with idiopathic interstitial lung disease in whom crocidolite fibers can be shown on electron microscopy of an open lung biopsy specimen.

How do asbestos fibers exert their tissue-damaging effects? Wilson has studied complement activation by these fibers using glutathione-sensitive lysis of human erythrocytes as an assay for complement activation.[7] He found that three different types of asbestos fibers caused lysis of human erythrocytes, which in this model implied an activation of the alternate complement system. In fact, one does not observe the same phenomenon with silica. Similarly, Wilson showed that asbestos fibers could cause a complement-activated chemotactic migration of human leukocytes. Again, silica does not cause such a complement-activated chemotaxis.

Epidemiologic studies have shown that with increasing exposure, the likelihood of asbestosis increases; that is, there is a dose-response relationship. However, in severe cases there is clearly a host-susceptibility factor. There is something peculiar about patients with severe asbestosis in terms of their response to injury. Turner-Warwick evaluated antinuclear antibodies (ANA) in various interstitial lung diseases.[8] Compared with persons having had similar exposure but with no disease, workers with asbestosis have a significantly in-patients with positive ANA who were followed for five years were more likely to show progression of years were more likely to show progression of disease than similarly exposed workers without positive ANA. It was felt that this nonorgan-specific antibody acts as an accelerator for the development of interstitial inflammation and fibrosis. Others have examined the relationship of the histocompatibility locus and have found that there is a greater incidence of HL-A B27 among workers with asbestosis than in exposed workers without manifestations of disease.[9] Finally, several investigators have examined T-cell function in persons with asbestosis.[10-12] Delayed skin tests to antigens such as streptokinase are often negative in persons with asbestosis compared with matched controls without disease. Kang found a decreasing percent of T-lymphocytes correlating with an increasing radiologic category of pulmonary asbestosis. He also reported a decreased lymphocyte response to phytohemagglutinin in workers with asbestosis. Kagan similarly reported abnormal T-cell function among workers with asbestosis as compared with similarly exposed workers without disease.

The use of pulmonary function testing to help identify asbestosis is a confusing matter. First, it is important to decide what exactly one wishes to determine by pulmonary function tests. That is, is one lookng for restrictive lung disease in an asbestos worker, or trying to assess disability? Other issues include pulmonary function changes with time and early detection of potentially affected workers. Classic findings from pulmonary function tests in persons with asbestosis have three characteristics typical of restrictive lung disease regardless of cause. First, there are small lung volumes. The vital capacity is reduced, as is the total lung capacity. Becklake has shown

TABLE 1.—*Characteristic Abnormalities Found on Exercise Testing With Interstitial Lung Disease, Including Asbestosis*

Pattern of Ventilation
Small tidal volumes
Hyperventilation in relation to oxygen consumption (reflex, partial pressure of oxygen and so forth)
High dead space/tidal volume ratio (V_D/V_T)
Efficiency of Oxygen Transfer
Increasing alveolar-arterial oxygen difference

that temporal changes in the vital capacity reflect progression of disease accompanying increasing asbestos exposure.[13] The second criterion is decreased diffusing capacity for carbon monoxide. The diffusion of carbon monoxide is its transport across the alveolar epithelium, the interstitial space, the capillary endothelium, the plasma and into the red cells where it combines with hemoglobin. The pathologic features in asbestosis involve a thickened or destroyed alveolar-capillary membrane which restricts the rate at which carbon monoxide reaches red cells, resulting in a diminished diffusing capacity. The third characteristic of any restrictive lung disease is increased flow rates. On screening pulmonary function tests, increased flow rates are reflected in the flow volume curve. Increased flow rates result from stiff lung due to the interstitial lung disease. Using an esophageal balloon one can measure the increased transpulmonary pressure necessary to inflate the lungs. Such stiff lungs have low compliance or a high recoil pressure so that flow rates are abnormally increased on exhalation.

How does one make the diagnosis of asbestosis? First, one should obtain the patient's history of exposure and history of dyspnea, initially with exercise only. On physical examination, clubbing of fingers and end-inspiratory crepitations at the bases of the lungs may be found. Radiographic examination may show irregular opacities. Finally, screening pulmonary function studies with the patient at rest may show restriction. However, it is possible for a patient to have shortness of breath ascribed to asbestosis well before resting pulmonary function test findings are abnormal.

In this regard, exercise testing should be men-

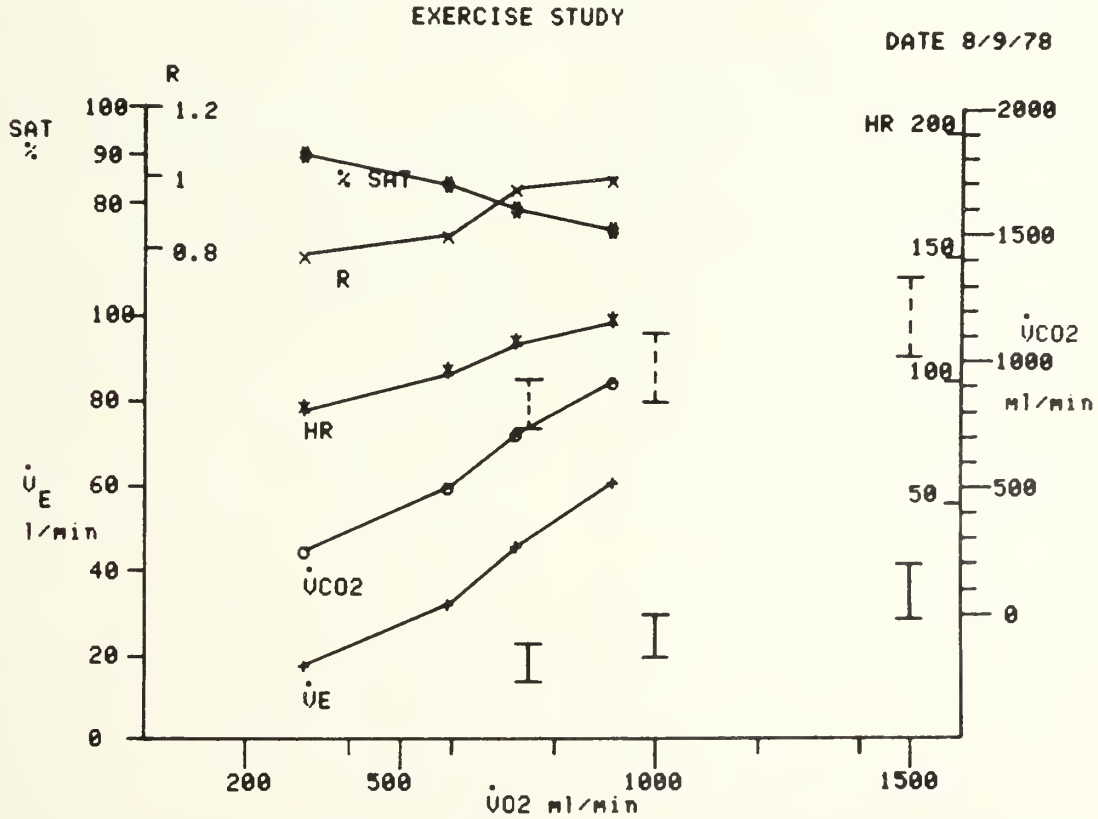

Figure 3.—Bloodless exercise study using ear oximeter showing desaturation of arterial blood and hyperventilation with increasing work load. $\dot{V}_E$ = minute ventilation; SAT% = arterial oxygen saturation; $\dot{V}O2$ = oxygen consumption; $\dot{V}CO2$ = carbon dioxide production; HR = heart rate; R = respiratory quotient (study courtesy of Andrew Binder, MD).

tioned.[11] Severe functional impairment may exist that is not detectable by a resting pulmonary function test but can be brought out by stressing the pulmonary system with exercise. In addition, one must discuss exercise testing when considering the issue of disability. The relationship of lung function (judged by lung volumes), lung failure (determined by blood gas measurements) and physical disability (gauged by the symptoms perceived by the patient) is not linear. It should be emphasized that there is no resting pulmonary function test that can predict disability with exercise. Exercise testing must be carried out to assess disability and to determine a mechanism of disability in terms of restrictive pulmonary physiology. For exercise testing, a patient exercises on a bicycle ergometer, and blood gases and exhaled gases are analyzed simultaneously at progressively increased work loads. In normal persons with increasing exercise, ventilation increases linearly with increasing oxygen uptake. With increasing exercise tidal volume increases, and the ratio of dead space to tidal volume diminishes. Finally, as a monitor of the efficiency of gas exchange one finds that the partial pressure of oxygen (Po_2) with increasing exercises remains the same, as does the alveolar-arterial Po_2 difference. With interstitial lung disease, such as in asbestosis, ventilation is increased greatly out of proportion to the work load; arterial oxygenation falls dramatically with increasing exercise as those poorly ventilated portions of the lung that had not been perfused at rest become perfused with exercise. This results in increasing alveolar-arterial Po_2 difference. Table 1 lists criteria of interstitial lung disease that may be brought out by exercise testing in a patient in whom resting pulmonary function findings are normal. Using an ear oximeter one can conduct a bloodless exercise study and show that there are oxygen desaturation and hyperventilation out of proportion to work load (Figure 3).

It is important to note that exercise testing can suggest other diseases as a cause of disability. A recent case illustrates a classic problem of determining disability in persons exposed to asbestos. The patient was a cigarette smoker with some obstructive lung disease. Radiographic examination showed small calcified plaques. On exercise, the minute ventilation was appropriate for increasing work load. Furthermore, the alveolar-arterial difference was not large and fell with exercise. In fact, an improving alveolar-arterial oxygen difference on exercise is consistent with chronic bronchitis. In this case we were able to conclude that the patient had been exposed to asbestos—however, pulmonary function on exercise was that of a person with chronic bronchitic changes.

The last manifestation of asbestos exposure we will consider is mesothelioma of the pleura or peritoneum. Mesotheliomas may arise following only brief exposures, but require a 20 to 30 year incubation period. Even household contacts are at risk.[15] It is distinctly unusual for a mesothelioma to occur without an associated pleural effusion. As to therapy, there are no cures for mesothelioma[16] and, in fact, there is no convincing evidence that even palliation is effective. There is no effective therapy and, because so many patients with mesothelioma die within a year after diagnosis, it is not clear that aggressive diagnostic procedures are indicated. Taking a pleural biopsy specimen can be justified, however, to rule out treatable causes of pleural effusion, such as tuberculosis. Also, of course, there are other malignant conditions associated with asbestos exposure, particularly bronchial carcinoma and carcinoma of the larynx and gastrointestinal tract.

REFERENCES

1. Becklake MR: Asbestos-related diseases of the lung and other organs—Their epidemiology and implications for clinical practice. Amer Rev Respir Dis 114:187-227 1976

2. Laamanen A, Noro L, Raunio V: Observations on atmospheric air pollution caused by asbestos. Ann NY Acad Sci 132: 240-254, 1965

3. Selikoff IJ, Anderson HA: Pleural reactions to environmental agents. Fed Proceedings 37:2496-2500, 1978

4. Gaensler EA, Kaplan AI: Asbestos pleural effusion. Ann Intern Med 74:178-191, 1971

5. Siemsen JK, Sargent EN, Siegfried FG, et al: Pulmonary concentrations of Ga^{67} in pneumoconiosis. Am J Roentgenol 120: 815-819, 1974

6. Miller A, Langer AM, Teirstein AS, et al: Nonspecific interstitial pulmonary fibrosis—Association with asbestos fibers detected by electron microscopy. N Engl J Med 292:91-93, 1975

7. Wilson MR, Gaunmer HR, Salvaggio JE: Activation of alternate complement pathway and generation of chemotactic factors by asbestos. J Allergy Clin Immunol 60:218-222, 1977

8. Warwick MT, Haslam P: Antibodies in some chronic fibrosing lung diseases—I. Non organ-specific autoantibodies. Clin Allergy 1:83-95, 1971

9. Merchant JA, Klouda PT, Souta CA, et al: The HL-A system in asbestosis workers. Br Med J 1:189-191, 1975

10. Kagan E, Solomon A, Cochrane JC, et al: Immunologic studies of patients with asbestosis—I. Studies of cell mediated immunity. Clin Exp Immunol 28:261-267, 1977

11. Kagan E: Immunologic studies of patients with asbestosis —II. Studies of circulating lymphoid cell numbers and humoral immunity. Clin Exp Immunol 28:268-275, 1977

12. Kang K-Y, Sera Y: T lymphocytes in asbestosis (Correspondence). N Engl J Med 291:735-736, 1974

13. Becklake MR, Fournier-Massey G, Rossiter CE, et al: Lung function in chrysotile asbestos mine and mill workers of Quebec. Arch Environ Health 24:401-407, 1972

14. Jones NL: New tests to assess lung function: Exercise testing in pulmonary evaluation—Rationale, methods and the normal respiratory response to exercise. N Engl J Med 293:647-650, 1975

15. Champion P: Two cases of malignant mesothelioma after exposure to asbestos. Am Rev Resp Dis 103:821-826, 1971

16. Chaninian AP, Holland JF: Treatment of diffuse malignant mesothelioma—A review. Mt Sinai J Med 45:54-67, 1978

Important Advances in Clinical Medicine

Epitomes of Progress — Anesthesiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in anesthesiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in anesthesiology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Anesthesiology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Serum Potassium and Anesthesia

THE SERUM POTASSIUM concentration of surgical patients is of critical concern to anesthesiologists because of its effect on myocardial function. Potassium ions are the most important cations for maintaining resting membrane potential and repolarization of the cardiac cell. Furthermore, myocardial contractility is influenced by intracellular potassium concentration.

Potassium ions are 200 times more permeable (that is, mobile) than sodium across the cell membrane. This means that serum potassium concentrations are easily influenced by disease states, preoperative drug therapy, anesthetic management and the acid-base status of a patient. Potassium is the predominant intracellular cation while sodium is the predominant extracellular cation. The resting membrane potential is maintained by the transmembrane potassium concentration gradient of about 155 mEq per liter inside and 4 mEq per liter outside.

Clinically, only the serum potassium is easily measured, which may give rise to erroneous interpretation and mismanagement of the patient since it may not reflect the total potassium content of the body. Serum alkalemia is the most common cause of relative hypokalemia. When serum alkalemia is produced by hyperventilation (respiratory alkalosis) or by increased serum bicarbonate (metabolic alkalosis), the body attempts to compensate by increasing the number of hydrogen ions in the extracellular space and increasing renal excretion of bicarbonate ions. The former is a more immediate physiologic compensatory mechanism. The source of hydrogen ions recruited is from the intracellular compartment at the expense of an exchange with potassium ions from the extracellular compartment. Therefore, serum alkalemia can lead to hypokalemia without immediate loss of potassium from the body. Serum acidemia tends to produce a relative hyperkalemia through a reversal of the potassium-hydrogen ion exchange. Acute reduction of serum potassium, without loss of body potassium, is not detrimental to the cardiovascular system. However, in patients whose total body potassium has been depleted by diuretics, digitalis, gastrointestinal loss or endocrine disorders, sudden reduction in serum potassium from hyperventilation can produce serious cardiac dysrhythmias. Furthermore, most of the drugs (including anesthetics) administered by an anesthesiologist are cardiovascular depressants and they can potentiate the

already reduced cardiac output from cardiac dysrhythmias.

Acute increases in serum potassium can lead to cardiac conduction block and arrest. Acute hyperkalemia may be caused by inappropriate exogenous administration of potassium chloride or the use of succinylcholine for muscle relaxation in patients who are severely burned, traumatized or have spinal cord injuries. When the serum potassium is allowed to accumulate in the body from lack of elimination (that is, renal failure), the potassium ions tend to distribute in body compartments maintaining the normal transmembrane potassium concentration gradient. Therefore, in chronically hyperkalemic patients elevated serum potassium levels tend to be tolerated far better than in normal patients whose serum potassium concentration is subjected to an acute rise. Nevertheless, a serum potassium value greater than 10 mEq per liter usually leads to cardiac arrest regardless of whether the hyperkalemia is acute or chronic.

In summary, both hypokalemia and hyperkalemia can disturb electrophysiology and induce cardiac failure. It is important to accurately determine the cause of the serum potassium abnormality in order to institute appropriate management.

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REFERENCES

Woodbury JW: Cellular electrophysiology of the heart. *In* Hamilton WF (Ed): Handbook of Physiology, Vol 1: Circulation. Washington, DC, American Physiological Society, 1962, pp 237-286

Scribner BH, Burnell JM: Interpretation of the serum potassium concentration. Metabolism 5:468-479, 1956

Wong KC: Electrolyte disturbance and anesthetic considerations. ASA Refresher Courses in Anesthesiology, Vol 6, 1978

Gronert GA, Theye RA: Pathophysiology of hyperkalemia induced by succinylcholine. Anesthesiology 43:89-99, Jul 1975

Local Anesthetic Agents in Obstetrics—An Update

THE USE OF local anesthetic agents to relieve the discomfort of the parturient during labor and delivery is common practice. We have in our armamentarium a choice of paracervical, paravertebral, epidural or caudal block to provide analgesia during labor, and we may utilize pudendal, subarachnoid (saddle), epidural, caudal or field block to provide perineal anesthesia for delivery. In the last decade there have been major advances in our understanding of the effects of local anesthetics on both fetuses and neonates. For example, we now realize that local anesthetics may readily cross the placenta and produce undesirable responses in a fetus. Second, more sophisticated methods are available to study the subacute effects of local anesthetics on neonatal neurobehavioral function.

The initial interest in fetal and neonatal blood levels of local anesthetics was generated by studies documenting the occurrence of fetal bradycardia following paracervical block and a possible correlation of this event with blood levels of local anesthetics. Subsequent evidence suggests that the mechanism of fetal bradycardia associated with this procedure may be hypoxia caused by local anesthetic-induced uterine artery vasoconstriction. Consequently, paracervical block is losing popularity, and most recent investigations are concerned with epidural and caudal anesthesia. With these latter blocks, significant amounts of local anesthetic can be absorbed by the engorged epidural venous plexus of pregnancy. Similarly, pudendal block and local infiltration of the perineum may also result in significant uptake of local anesthetic into the maternal bloodstream due to the vascularity of the area. Moderate caution should be applied to these techniques.

When selecting an amide-type of local anesthetic agent requiring slow hepatic degradation, consideration should be given to those properties of the drug that allow for transfer from the maternal circulation across the placental membrane to the fetus. In addition, attention should be paid to the disposition and metabolism by the fetus and neonate because this determines ultimate toxicity. Substances that are highly bound to plasma proteins have less free drug available for transfer. Highly ionized or charged compounds do not cross membranes easily. Drugs which are highly lipid-soluble do cross membranes easily, but this same quality may allow for deposition in epidural adipose tissue, thereby decreasing the maternal level. In addition, because of rapid penetration into fetal fat compartments, the fetal blood level is also decreased.

The duration of action is important because the longer-acting agents tend to decrease the total quantity of drug required. Lidocaine and mepivacaine are considered intermediate in action with a duration of 45 to 75 minutes, while the long-acting bupivacaine (Marcaine) has a usual duration of 1½ to 2 hours. The short-acting ester 2-chloroprocaine (Nesacaine) has an average duration of 45 minutes. An additional advantage is its rapid rate of destruction by plasma cholinesterase and a half-life of 21 seconds. Little if any will be available for placental transfer. The

fetus also has plasma cholinesterase activity present as early as 28 weeks of gestation.

The neurobehavioral assessment scale, for use in evaluating subtle neonatal behavioral alterations induced by anesthetic drugs and the events of labor, was introduced in 1973 by Brazelton and recently modified by Scanlon. This complex system allows far more accurate assessment than by Apgar scoring alone. Neurobehavioral assessment of infants of mothers who received local anesthetic drugs in epidural anesthetics for labor and delivery shows that when lidocaine and mepivacaine were used the infants had poorer muscle tone scores and habituation to pinprick at 2 and 4 hours of age. With the use of bupivacaine or 2-chloroprocaine, scores were equal to or better than those in control infants. It is important to note, however, that all infants were the same by the second day of life. No long-term inferences can be made at this time.

The current recommendations for use of local anesthetic drugs in regional anesthesia for obstetrics are to utilize the minimum amount of drug needed to produce the desired effect and to avoid those agents and techniques that cause measurable changes in the fetus or the neonate. Based on the foregoing considerations, epidural or caudal anesthesia with 2-chloroprocaine or bupivacaine (or both) fulfills these requirements.

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REFERENCES

Ralston DH, Shnider SM: The fetal and neonatal effects of regional anesthesia in obstetrics. Anesthesiology 48:34-64, Jan 1978

Scanlon JW, Ostheimer GW, Lurie AO, et al: Neurobehavioral responses and drug concentrations in newborns after maternal epidural anesthesia with bupivacaine. Anesthesiology 45:400-405, Oct 1976

Management of Patients With Increased Intracranial Volume or Pressure

THE CRANIAL VAULT is a semi-closed cavity containing brain, blood and cerebrospinal fluid. These three components do not under normal circumstances completely fill the cavity. Rather, there is room available for expansion. Intracranial pressure (ICP) is normally less than 10 torr. ICP does not rise until increases in cranial contents have completely filled the cranial vault. Then, even slight increases in intracranial volume cause steep increases in ICP. Common causes of an increase in volume are brain tumors, posttraumatic swelling, vasodilatation with increased cerebral blood flow or blockage of cerebrospinal fluid drainage. As ICP rises, a critical lowering of the cerebral perfusion pressure can occur and produce cerebral hypoxia. The mean arterial pressure minus the ICP is the cerebral perfusion pressure. There are compensatory mechanisms that can blunt or reverse elevations in ICP. Compensation can occur through cerebral vasoconstriction, brain shrinkage, reduction of cerebrospinal fluid production and relocation of cerebrospinal fluid in the spinal canal.

The treatment of patients with increased intracranial volume makes use of these compensatory mechanisms and must prevent further increases in volume. Respiratory obstruction or depression must be immediately corrected. Carbon dioxide retention produces cerebral vasodilatation as does hypoxemia if arterial oxygen tension falls below 50 torr. Dilatation from hypoxemia is more serious and troublesome than carbon dioxide retention due to its persistence after the hypoxemia has been corrected. Vasodilatation from carbon dioxide retention increases cerebral blood flow 1 ml per 100 grams of brain tissue per minute for each 1 torr rise in arterial carbon dioxide pressure. However, hyperventilation to produce hypocapnia is immediately beneficial as a reduction of cerebral blood flow of 1 ml per minute is achieved with each 1 torr decrease in carbon dioxide pressure. Additional increases in brain volume can be prevented by fluid restriction and the avoidance of 5 percent dextrose in water solutions. Dextrose in water is rapidly absorbed into brain cells carrying water with it. Stabilization of the blood-brain barrier with large doses of steroids, usually dexamethasone, also inhibits swelling. Brain bulk can be reduced through cerebral dehydration with osmotic and renal diuretics such as mannitol and furosemide. Methods of decreasing cerebrospinal fluid production are less well defined, although steroids may decrease production.

Reduction of cerebrospinal fluid volume should only be done at surgical operation. Spinal taps are to be condemned because danger of herniation of the brain is real and little helpful information is obtained. During surgical operation, the head-up position and avoidance of jugular vein compression enhance venous return. Volatile anesthetic agents cause cerebral vasodilatation proportional to their anesthetic depth and, therefore, should be avoided or administered at very light levels only after hypocapnia has been established and verified. Monitoring of arterial blood gases and

pressure is aided by arterial cannulation and is highly recommended.

FLOYD S. BRAUER, MD

REFERENCES

Albin MS: Anesthetic management of the patient with head injury. Int Anesthesiol Clin 15:297-307, Fall 1977

Shapiro HM: Intracranial hypertension—Therapeutic and anesthetic considerations. Anesthesiology 43:445-471, Oct 1975

Radial Artery Cannulation

RADIAL ARTERIES are cannulated for blood gas sampling, continuous blood pressure and pulse rate monitoring, pulse wave analysis, cardiac output determinations, phlebotomy, exchange transfusions, angiography and pulse triggering of intraaortic balloons. Thrombosis may occur in 60 percent of cannulated radial arteries. Even with complete occlusion, collateral circulation from the ulnar artery usually prevents ischemic complications. Assessment of the patency and distribution of ulnar artery collateral flow before radial artery cannulation is mandatory. Collateral flow can be measured by the modified Allen test, finger plethysmography or Doppler flow studies. In three percent of the population, collateral flow is inadequate and radial artery cannulation is contraindicated.

Measurement of wrist circumference is a reliable predictor of the risk of vascular occlusion developing. The smaller the wrist, the smaller the radial artery and the greater the likelihood of subsequent thrombosis. If the wrist circumference is less than 16 cm, the radial artery should be cannulated with small (20-gauge) catheters. The incidence of radial artery thrombosis is also directly related to the size, shape, and composition of the catheter used. In adults, 20-gauge catheters are associated with fewer cases of thrombosis than 18-gauge catheters. Untapered catheters are safer than those with tapered shafts. Teflon catheters have a lower incidence of thrombosis than similar polypropylene catheters. Finally, the occurrence of radial artery thrombosis is directly proportional to the duration of cannulation, so catheters should be removed as soon as they are no longer needed. Intermittent or continuous infusion of dilute heparin solution will prolong the patency of indwelling catheters but will not prevent eventual thrombosis. Concentrated heparin solutions will cause arterial vasoconstriction.

Care must be exercised not to inject air bubbles when flushing the catheter, and the flush solution must be injected in small volumes (less than 3 ml) at slow rates to avoid retrograde embolization of clot material to the carotid artery. Blood removed from the catheter should not be reinjected into the artery, but should either be discarded or placed into the venous system. Catheters should be aspirated for clots periodically and during decannulation. Catheter balloon thrombectomy can also be carried out if necessary.

Ischemic complications requiring thrombectomy occur in 0.2 percent to 0.6 percent of radial artery cannulations. No major vascular complications requiring amputation occurred in one series of 4,000 cannulations. Consideration of the factors discussed makes radial artery cannulation a safe procedure.

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REFERENCES

Hedley-Whyte J, Burgess GE II, Feeley TW, et al: Applied Physiology of Respiratory Care. Boston, Little, Brown and Co, 1976

Greenhow DE: Incorrect performance of Allen's test—Ulnar-artery flow erroneously presumed inadequate. Anesthesiology 37: 356-357, Sep 1972

Bedford RF: Wrist circumference predicts the risk of radial-arterial occlusion after cannulation. Anesthesiology 48:377-378, May 1978

Gardner RM, Schwartz R, Wong HC, et al: Percutaneous indwelling radial-artery catheters for monitoring cardiovascular function—Prospective study of the risk of thrombosis and infection. N Engl J Med 290:1227-1231, May 30, 1974

Banked Autologous Blood Transfusion

WITH THE INCREASING SCARCITY of stored banked blood, it is becoming apparent that a large proportion of patients with anticipated transfusion requirements can safely donate their own blood before elective operations.

The prior deposit of a patient's own blood avoids most of the hazards associated with homologous blood transfusions. Other advantages are stimulation of erythropoiesis and conservation of donor reserves. Excessive falls in the hemoglobin level to less than 10 grams per dl can be avoided with judicious iron therapy. Plasma volume is restored 32 to 76 hours after phlebotomy.

One unit of blood can be taken every four to seven days, up to 36 hours before an operation. The blood storage time limit of 21 days can be increased to 35 days by the use of citrate-phosphate-dextrose solution, and storage time is practically unlimited with frozen red blood cells. As identification errors are still possible, a fail-proof identification system is necessary, together with serologic tests and informed consent.

Suitable candidates for autologous transfusion include most elective surgical patients in reasonably good health, although patients with coronary, valvular or congenital cardiac disease have do-

nated up to 10 units of their own blood before surgical operation. The prephlebotomy hemoglobin level should be at least 11 grams per dl. Iron should be administered orally to these patients (325 mg of ferrous sulfate three times a day)—this is as effective as parenterally given iron and less hazardous.

Patients with rare blood types, those who are difficult to cross-match, those previously alloimmunized and candidates for transplant represent special indications. Contraindications are infections or neoplasia (risk of dissemination), inability to increase red cell production in response to iron therapy, sickle cell disease, and occupations requiring intense physical exertion or hazardous duties.

It is the physician's responsibility to inform his patient about this safe, readily available and well-tolerated procedure. Hospitals and medical staff organizations should be encouraged to develop active recruitment programs.

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REFERENCES

Brzica SM: Preoperative deposit, *In* Autologous Blood Transfusion Workshop. Audio-Digest, Anesthesiology 20:No 23, Dec 4, 1978

Fleming AW, Green DC, Radcliffe JH, et al: Development of a practical autologous blood transfusion program. Am Surg 43: 794-801, Dec 1977

Paternal Participation in Obstetrical Anesthesia

WE HAVE ENTERED an era of consumerism in medicine, especially in obstetrics. Physicians must be responsive to present-day needs in order to prevent patients from avoiding hospitals and seeking less conventional and less safe care.

It has become fashionable for fathers to be present during childbirth; this includes during labor, delivery and even cesarean section. Anesthesiologists should be aware of this and able to deal with the situation.

Whether to allow the father to be present during administration of an epidural anesthetic for labor is controversial. On the positive side, the father may be able to distract and reassure the mother. On the other hand, the father may be distressed by the large needles and occasional blood loss associated with this procedure and may respond adversely to the situation. The simplest solution is to politely ask the father to leave during the administration of the anesthetic, and to invite him to return once anesthesia has been well established. This may not necessarily be appropriate in all cases. Some fathers will become hostile if asked to leave and some, as mentioned previously, may even be helpful during the procedure. The ideal solution is to be sure there is good communication with the father and to allow him some freedom of choice.

If the father is to be present during administration of an epidural anesthetic, certain precautions must be taken to provide for his safety. We have had the experience of a father falling and fracturing his skull during the administration of an epidural anesthetic. If the father remains, he should be seated in a chair facing the mother. Further, his nutritional state should be determined. In the instance cited, the father had not eaten for many hours and was probably somewhat hypoglycemic and hypovolemic when overcome by the stress of the situation. We have found that most fathers who feel uncomfortable will leave the room voluntarily.

If delivery is to be by cesarean section, the situation becomes more complex. The idea of fathers being present during cesarean section has not been greeted with general enthusiasm by obstetricians and anesthesiologists. However, we must again be responsive to the needs of our patients. Many institutions have protocols that make the situation more manageable. In the first place, it must be understood by the father that he may be asked to leave at any time, either by the obstetrician or the anesthesiologist. There can be no question of this point. The father should attend some form of prepared childbirth classes, preferably those dealing directly with cesarean section. Although the question of whether fathers should be present during the administration of the anesthetic is controversial, the same considerations should apply here as during labor.

In either case, once anesthesia has been established and the mother positioned on the operating table, the father should be seated at the head of the table next to the anesthesiologist and behind the drapes. He should be reminded that he is there to support the mother and participate in the delivery and not to be an observer of surgical procedure. Again, he should be watched closely for signs of faintness. At delivery, he may be invited to the bassinet to observe the infant, and then back to the mother when the infant is brought to her. It is generally efficacious if he accompanies the infant to the nursery, which allows simpler management of the remainder of the surgical

procedure. He can then be reunited with the mother at the end of the operation.

Some institutions have a separate consent form for a father to sign if he is to be present during delivery. This may have some value in legal protection of the physician and institution. However, the best protection is a well-established rapport with the patient.

All of this may be viewed by some physicians as unduly complicating the practice of medicine. It must be remembered, however, that the practice of medicine is directed at the health of the patient. This health must be psychological as well as physical, and in many instances the presence of the fathers during an obstetrical procedure may be vital to the health of the family unit.

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REFERENCE

DeVore JS, Asrani R: Paternal fractured skull as a complication of obstetric anesthesia (Letter). Anesthesiology 48:386, May 1978

Implications of Opiate Receptors and Endorphins for Anesthesiologists

EARLY IN THIS DECADE (1973) nervous tissue receptors were identified that combine stereospecifically with known opiate agonists and antagonists. When opiates bind to these receptors, there is a conformational change which alters cell membrane function, perhaps due to an inhibition in adenylate cyclase activity. Naloxone, a pure antagonist, can also occupy the opiate receptor, but stabilizes it in an inactive conformation. Opiate receptors have been found in all vertebrate species including man, but not in invertebrates. Areas of the central nervous system having a high opiate receptor density include parts of the limbic system, medial thalamic nuclei, the periaqueductal gray and the substantia gelatinosa of the spinal cord.

Teleologically it seemed unlikely that vertebrate opiate receptors would have evolved to combine with plant alkaloids. Thus, by 1975, several groups discovered a variety of polypeptides now named endorphins (*endo*genous m*orphin*e-like substances). These included two pentapeptides now identified throughout the brain and spinal cord; these pentapeptides are also called enkephalins. Enkephalins are quite likely a new class of neurotransmitters whose function is barely understood.

Longer peptide (31 amino acids) endorphins were also located in the pituitary and brain. Interestingly, the amino acid sequence of the enkephalins is contained within the 31 amino acid (β) endorphin. In turn, the β-endorphin sequence is part of a 91 amino acid pituitary peptide, β-lipotropin. When enkephalins or β-endorphins are applied to nervous tissue, morphine effects result. Naloxone reverses all effects of exogenously administered endorphins.

The existence of endorphins or enkephalins with a neurophysiological role would demand that direct pharmacological actions of a pure opiate antagonist be seen. Yet traditionally, naloxone has been considered to have no important direct effects of its own, save to antagonize the actions of exogenous opioid drugs. The role of opioid peptides in narcotic addiction, mental illness, pain states and temperature regulation is being investigated. These studies start with the postulate that the pathological or experimental condition studied activates the endorphin system. Pharmacologic activity of naloxone under these conditions is taken as necessary, but not as sufficient evidence to prove endorphin mediation.

The same logic has been applied to studies of anesthesia. While an initial report observed naloxone reversal of general anesthesia, this has not been verified. The role of endorphins in the anesthetic state, therefore, remains undefined.

The discovery of opiate receptors in both brain and spinal cord has provided an understanding that morphine and other opiates act at both brain and spinal cord levels. In fact, the presence of spinal cord opiate receptors (probably inhibitory) has prompted the study of intrathecally or epidurally administered morphine; preliminary reports have shown efficacy in chronic pain states. One awaits a systematic verification of safety and efficacy in chronic and acute pain conditions (postoperative pain and first stage of labor).

The release of spinal cord enkephalins blocking relay of pain sensations is also a plausible explanation for the analgesia produced by traditional acupunture, electro-acupuncture and transcutaneous electrical nerve stimulation. Acupuncture analgesia has indeed been found reversible by naloxone. Conceivably, acupuncture might reduce the amounts of inhalational anesthetic required for general anesthesia and thereby increase patient safety. Finally, the well-known ability of placebo medications to provide significant analgesia also appears explainable by the enkephalin system.

The physiological roles of both opiate receptors

and endorphins, despite continuous and intense study, are still largely unknown. The manipulation of an internal analgesia control system by the anesthesiologist has great speculative appeal, but awaits further study.

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REFERENCES

Snyder SH: Opiate receptors in the brain. N Engl J Med 296: 266-271, Feb 3, 1977

Terenius L: Endogenous peptides and analgesia. Annu Rev Pharmacol Toxicol 18:189-204, 1978

Goldstein A: Enkephalins, opiate receptors, and general anesthesia. Anesthesiology 49:1-2, Jul 1978

Levine JD, Gordon NC, Fields HL: The mechanism of placebo analgesia. Lancet 2:654-657, Sep 23, 1978

Pace NL, Wong KC: Failure of naloxone and naltrexone to antagonize halothane anesthesia in the dog. Anesth Analg (Cleve) 58:36-39, Jan-Feb 1979

Neonatal Anesthesia

AN OPERATIVE PROCEDURE during the first few days of life superimposes the stress of anesthesia and surgical operation upon the normal stress of adaptation from fetal to neonatal life. Most reviews indicate the risk of anesthesia in the newborn infants is higher than in older children or adults.

Improved techniques and equipment have made anesthesia safer for newborn infants. Parallel advances in pediatric surgery and neonatology have broadened the range of surgical procedures and acceptable risks, providing anesthetists a challenge in dealing with severely ill and often quite premature infants with complicated medical problems. Anesthetic management of these patients has required refinement of techniques and miniaturization of equipment from adult anesthetic practice and the application of principles of neonatal intensive care in the perioperative period.

The greatest advance in neonatal acute care in the past decade has been in the management of infants with respiratory disorders, primarily the respiratory distress syndrome. Many factors including the use of constant distending airway pressure, improved ventilator design and diligent monitoring techniques, have contributed to improved survival rates. The application of these techniques during an operation and in the postoperative period has made major surgical procedures in neonates with respiratory impairment possible.

Risks inherent in such treatment have also appeared. The potential retinal toxicity of high oxygen tensions in the newborn period requires the inspired oxygen concentration be monitored and arterial oxygen tension maintained between 50 and 80 torr in any infant younger than 44 weeks of gestational age. Similar caution with oxygen administration should be maintained during an operation in these infants to minimize the risk of retrolental fibroplasia.

Routine intraoperative monitoring equipment for the newborn includes a precordial or esophageal stethoscope, a reliable device for accurately measuring blood pressure, an electrocardiograph and an oxygen analyzer for measuring the fraction of inspired oxygen (FIO_2) of anesthetic gas mixtures. The use of an indwelling umbilical or peripheral arterial catheter allows frequent measurement of arterial blood gases as well as continual monitoring of blood pressure. With the promising improvements in transcutaneous oxygen electrodes and photo-oximeters, a reliable noninvasive means of continuous oxygen monitoring will soon be available.

Cold stress, so frequently harmful to the premature infant undergoing surgery in the past, is greatly decreased in the modern operating room. Continuous temperature monitoring guides the regulation of body temperature with the use of a transport incubator, controlled operating room temperature, an overhead warmer, a circulating water mattress, warmed intravenous and irrigating solutions, and a heated humidified breathing circuit.

The treatment of metabolic disorders in newborn infants has been greatly simplified by the general availability of rapid microtechniques for determining values for serum electrolytes, glucose, calcium, bilirubin and arterial blood gases. It is the responsibility of anesthetists to assure that monitoring and correction of such metabolic disturbances continue during the perioperative period.

Controlled or assisted ventilation and endotracheal intubation have become routine for virtually all general anesthetics in the neonatal period. An uncuffed minimally reactive plastic Magill tube or a Murphy-type tube is used. Intraoperative fluids and blood replacement are given most accurately by syringe or controlled-rate infusion pump into an intravenous catheter or cannula. The miniaturization of the *catheter-over-needle* type of intravenous sets (now available in 22-gauge and soon in 24-gauge sizes) has made possible percutaneous placement of a reliable venous cannula in most newborn infants without requiring surgical cutdown. Similar cannulae are useful for percutaneous peripheral arterial cannulation. In newborn patients, this

technique is facilitated by transillumination of the extremity to visualize the artery.

The choice of anesthetic agents for neonates has evolved primarily by extrapolation from adult practice and through the experience of clinical anesthetists. Regrettably, few controlled experimental data exist concerning the effect of anesthetics on the human newborn. A number of studies have shown differences, both qualitative and quantitative, in the response of neonates to drugs. Full evaluation of newborn infants' response to the commonly used anesthetic agents will be of great value to anesthetists.

More intensive research in neonatal pharmacology and pathophysiology, further technical improvement and the general availability of personnel trained in pediatric anesthesia should continue to decrease the risk of anesthesia and surgical operations in newborn infants.

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REFERENCES

Downes JJ, Betts EK: Anesthesia for the critically ill infant. ASA Refresher Courses in Anesthesiology 5:47-69, 1977

Betts EK, Downes JJ, Schaffer DB, et al: Retrolental fibroplasia and oxygen administration during general anesthesia. Anesthesiology 47:518-520, Dec 1977

Hackel A, Bland JW, Schwartz AJ: Monitoring the pediatric patient. ASA Annual Refresher Course Lectures 220:1-14, 1978

Bennett EJ, Patel KP, Grundy EM: Neonatal temperature and surgery. Anesthesiology 46:303-304, Apr 1977

Udkow G: Pediatric clinical pharmacology. Am J Dis Child 132:1025-1032, Oct 1978

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EDITORIALS

The Accreditation of Continuing Medical Education

THE SUDDEN AND DECISIVE ACTION of the AMA House of Delegates in July, which then and there terminated the participation of the American Medical Association in the Liaison Committee on Continuing Medical Education (LCCME), has added new confusion to a situation that was already pretty confused. Are there now to be two national accrediting bodies for continuing medical education? The AMA's Immediate Past President, Tom E. Nesbitt, told the House "It's time to bring CME back into the fold of the AMA, where it belongs." This may be true. Accreditation of CME had been the province of the AMA for a decade until 1977 when by agreement among all concerned this responsibility was transferred to the LCCME, which was sponsored jointly by the American Medical Association, the Association of American Medical Colleges, the American Board of Medical Specialties, the Council of Medical Specialty Societies, the American Hospital Association, the Association for Hospital Medical Education and the Federation of State Medical Boards. It is noteworthy that each of these organizations was recognized as having a legitimate interest in the accreditation of continuing medical education programs for practicing physicians. However, in reality the AMA provided the largest portion of the staffing and financial support for the LCCME.

Difficulties to which this writer is not privy must have arisen. It is widely known that there were disagreements between the LCCME and the state medical associations, many of which had been recognized in regard to CME by their state licensing boards. And there may have been some intransigence. But now it is possible that the AMA's accreditation of CME may be recognized only by itself and its component state medical associations, unless it can find ways to take into account the legitimate interests of some of the other organizations. This would certainly be divisive for medicine at a time when we can ill afford division.

But what is really at stake in all of this is the need to provide some real accountability for the quality of continuing medical education programs for the practicing physicians who may wish to participate in a course or program, and for the public which wishes some assurance that a physician's continuing education is meaningful and relevant to the needs of practice. The parties at interest to all this are not only the practicing physicians and the public (including government), but the educators in medical schools, specialty societies and specialty boards, and the hospital providers of CME as well as various other physicians' organizations. Much time and effort has been spent by many of these groups (including the AMA) seeking to improve and assure the quality of CME programs. Most agree that a national accrediting body in the private sector is desirable, and that while the accrediting authority may have to be delegated, this should be within broad guidelines agreed upon by the parties at interest and formalized by the national accrediting body.

Continuing medical education has grown up and matured considerably in the last three years. There are many new forces at work which were not so evident even in 1977. The AMA Council on Medical Education has now been given a large task, a task acquired by fiat, rather than by consensus or agreement. Wisdom, skill and statesmanship will all be required in good measure.

—MSMW

New Perspectives in the Treatment of Hypertensive Patients

JUST WHEN YOU THINK you have learned more about a subject than you really care to know, someone teaches you something new and different. The paper "Nontraditional Problems of Anti-

hypertensive Management" by Peter Rudd and Keith Marton, which appears elsewhere in this issue, offers a fascinating new approach to hypertension. When I saw the title I had that sinking feeling, "Oh no, not another preachy bit about hypertension." But I plowed into it and soon found myself intrigued. This paper could be subtitled "All the *other* things you have thought about hypertension, but never found in one place."

The authors have attacked hypertension from an offbeat angle—its social and psychological effects on patients and physicians—and by the last page you are thoroughly depressed about the whole matter. The discussion is divided into sections on patient screening, disease labeling, diagnosis confirmation, patient compliance and physician adherence.

The section on patient screening describes the poor results from screening operations that occur in most communitywide efforts; few original cases are uncovered with this method. Most of those who come for testing are persons who already have been told they have hypertension or have a family history of the disease; some *cases* turn out to be noncases of labile hypertension (52 percent). The authors cite several reasons: arbitrary limits of abnormality are either too sensitive (false positive) or too insensitive (false negative), or blood pressure variations may be due to equipment or observer problems. Finally, there is the discouraging problem of loss of those truly hypertensive patients who fall between the cracks on follow-up.

"Disease labeling" discusses the serious problems faced by persons who are labeled as "hypertensive." A fascinating fact emerges: asymptomatic patients (previously ignorant of the fact that they have hypertension) suffer a three-fold increase in absenteeism *after* they are told—according to one study. This is 1½ times greater than for those who were previously aware that they had hypertension. Curiously, absenteeism was lowest among untreated, previously aware persons. The rise in absenteeism was associated with treatment, noncompliance and vigorous educational efforts; it was not related to blood pressure control. It is noted that possible causes for this behavior are a lowered "self-concept" and deterioration of marital and home satisfaction. Such patients were observed to consider themselves "more fragile and debilitated." The authors caution that these findings are from a single study and that studies should be done among other types of workers in other environments.

Every clinician who has dealt with hypertensive patients is familiar with this psychologic phenomenon. It occurs in other diseases that are asymptomatic in their early phase, but which have serious long-term sequelae unless effective treatment is instituted and sustained. In the situation of asymptomatic hypertension, we typically have a person who has considered himself healthy. Suddenly, perhaps as the result of a routine physical examination, he is "educated" about his disease: a life-threatening condition that can cause a heart attack or stroke unless he remains on treatment the rest of his life. And to compound the problem, the treatment often causes unpleasant symptoms.

It is difficult to conceive of a more disturbing situation. It demands effective, sympathetic discussion by the clinician to persuade the patient intellectually *and* emotionally about the importance of sustaining the treatment. Yet the clinician must not alarm him and create an emotional cripple. It is not an easy task, and the psychological trauma plus the poor compliance that abounds with this disorder, indicate that physicians are not doing this job well.

Rudd and Marton continue their depressing presentation by describing the increased life insurance premiums for patients labeled hypertensive, which only reinforce the sense of alarm and loss of self-image.

The authors cite the critical need to ensure that the patient does, indeed, have significant, nonlabile hypertension. They state that, despite the Framingham study which correlated *systolic* pressure elevations with congestive heart failure, coronary artery disease, cerebrovascular accidents and electrocardiographic changes, tradition dictates that we treat the diastolic pressure. (Most clinicians have tended to ignore all but the most extreme levels of systolic blood pressure in older folks because of the disabling effect of drug-induced hypotension.) The authors discuss the problems of variations in technique that cause difficulty in establishing the diagnosis: wrong-sized cuff, confusion over whether to listen to phase 4 or phase 5 Karotkoff sounds, observed variation and lack of proper manometric calibration (especially the volatile aneroids). All tend to cause more false-positive observations than false negatives.

As anticipated, the authors reopened the Melby (comprehensive initial workup for all hypertensive persons) versus the Gifford and Finnerty (treat them all, and if there is no response, or if they fall into a special category, *then* do the extensive

workup) controversy. Rudd and Marton favor the latter approach, citing the rarity of curable hypertension and frequent failures after surgical manipulation of renovascular hypertension. I share their view: costs of universal extensive diagnostic workup are prohibitive in this era of cost accountability. *Correctable* diagnosis can be suspected by careful clinical evaluation and minimal laboratory examination.

A detailed and enlightened discussion of the critical problem of *patient compliance* is a high point. In my experience there is no substitute for a zealous nurse with a hot telephone to tweak those hypertensive patients who miss appointments. They must be hounded to discover whether they have become ill, whether the medication is causing embarrassing or otherwise undesirable adverse side effects or whether they are simply too embarrassed to come in because they have failed to take the medication. Compliance is a function of physician perseverance and determination.

As stated earlier, patients must be intellectually and emotionally convinced to continue life-long therapy, yet they cannot be alarmed into disability. The authors also make the key point that therapeutic programs must be kept as simple as possible and tailored to the life-style of the patient. All clinicians have found it valuable to have blood pressures taken at home by reliable family members who are involved with the patient personally and who are convinced of the importance of sustained treatment.

The final section of the paper, on professional variability, presents an incredible array of physician *malfunctions*. These range from poor (or absent) record keeping, failure to recognize hypertension, casual attitude about patient education and failure to pursue those patients who are not cooperative.

The problem of educating physicians about hypertension is real. There is a certain apathy among clinicians about diseases that have few obvious symptoms yet which cause damage at a subtle, nondramatic pace (until the patient gets a myocardial infarction or suffers a stroke). It is an especially unappealing situation when an asymptomatic patient is obliged to take medication that may make him unhappy or even sick. It is a no win situation in the short haul; but in hypertension it is the long haul that is important.

After this doleful recitation the authors nibble at the solution to the problems in two concluding paragraphs. Once again they cite the importance of physician education as the chief factor in solving this multitude of nontraditional pitfalls.

It is a thoroughly readable paper, and it is referenced with a vengeance.

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A New Kind of Melting Pot

SUMMER IS A TIME for reflection and even some dreaming. The slackened pace, if one is lucky enough to have it slacken, provides an occasional moment when one can stand back and look at the forest made up of all the trees that come to one's attention in the course of daily events. For example, if one stands back, reflects and dreams, one might sense that America may be creating a new kind of melting pot, with a new place in the world—with new responsibilities and opportunities for medicine.

America has long been described as a melting pot. For years it was able to absorb and integrate wave after wave of immigrants, primarily from Europe. Most of these entered the country legally and earned their place in American society by working long and hard, as indeed did the earlier settlers who developed the principles of freedom, enterprise and law which served to make the nation great—in fact the envy of the world. Our industrial products were the mark of a new standard of living among even the more advanced nations, and American efficiency was what made this production possible on such a scale. Even today our know-how and expertise are courted by other nations, including the USSR and the People's Republic of China as these nations seek to improve the standard of living of their peoples. The American dollar was pegged to gold and the expression *sound as a dollar* meant something more than it does today.

But this kind of a melting pot seems to have passed its zenith and to be approaching some kind of nadir if one uses only the above criteria. Illegal aliens abound, particularly in the West and parts of the South. Many of these people work hard but do not pay taxes, and many require support through our public programs. Illegal entry of persons and contraband seems to occur almost as if the borders did not exist. Persons of Mexican birth or ancestry will soon be a

majority in many parts of the Southwest, and this will amount to a kind of extension of that country into the United States. The work ethic is clearly changing as everyone tries to get more for working less, and as we give various groups in the population special competitive advantages to compensate for educational or other disadvantages. The two major countries we defeated in World War II have recovered with our help and are now efficiently outproducing us—beating us at our own game, as it were. For example, better and more efficient foreign automobiles are outselling American ones in the American market, clearly a change from what used to be the case. A persistent foreign trade deficit, worsened by the oil crisis, has replaced a favorable balance. Foreign capital is now being invested in the United States on a growing scale, favored by the relative cheapness of the dollar—with potential for good and bad that is unpredictable at this time.

It would seem that the so-called American melting pot is moving from its former and familiar independence to unfamiliar interdependence. It seems inevitable, as time goes on and with things being the way they are, that "foreigners" will control more and more of our land, our capital, our business and industry, and our political system. As this occurs America's melting pot will come to have more international dimensions. It is noteworthy that this will be at a time when other nations, including those of the Third World, will join China and Russia in striving to reach the kind of living standard America has shown to be possible, and then they too will have all the problems of its success—inefficiencies due to overregulation, underproductivity, environmental pollution and unavoidable dependence for some essential resources upon other nations which may or may not be cooperative.

If this is to occur, where is there a role for medicine? Health, well-being and personal fulfillment are essential ingredients of the higher standard of living that a new worldwide melting pot will strive to achieve. They are also what physicians seek for their patients and for the public. Medicine with all its branches and ramifications is the human life science for health, well-being and personal fulfillment, and physicians together with other health professionals profess and practice this science and its art in the human society. If, when and as the American melting pot goes international, there will surely be new opportunities and responsibilities for American medicine throughout the world as well as at home. It certainly is not too early to dream—and it may not be too early to think and even begin to plan.

—MSMW

Rheumatic Disease—A Case of the Soil and the Seed

A SMALL RENAISSANCE is occurring in clinical rheumatology. This is largely due to better recognition of two distinctive forms of rheumatic disease. Identification of the various arthropathies associated with calcium pyrophosphate deposition disease has thrust this cartilage disorder to the fore.[1] Also, a cleaner delineation of the seronegative spondyloarthropathies as a group of diseases "running in families" has led to the realization that many examples of *forme fruste* rheumatic disease belong in this category.[2] Dr. Calin's article elsewhere in this issue focuses on this latter group of diseases and, in so doing, indicates how the recognition of a genetic susceptibility to acute or chronic rheumatic disease naturally leads to better or earlier diagnosis, as well as to a more scientific pursuit of pathogenesis.

Diagnostic criteria might well be considered to be the Achilles' heel of rheumatology. So many forms of arthritis lack objective and distinctive markers. Recognition of the association between the seronegative spondyloarthropathies and HLA-B27 has led to a widening of our diagnostic horizons and has pointed to the need for reappraising many conventional clinical criteria for identifying ankylosing spondylitis and the Reiter syndrome. As Dr. Calin indicates, epidemiologic data on this group of rheumatic diseases will now have to be reexamined using broader criteria including tissue typing as well as radiographic and scintigraphic methods. Indeed the old accepted adage of "radiographic sacroiliitis equals ankylosing spondylitis" needs to be reappraised, and more sensitive diagnostic tests should be designed to detect preradiographic osteoarticular inflammations.

The main theme of Dr. Calin's article is that rheumatic disease results from an interaction between a genetically predisposed host and environmental factors—the "soil and seed." This concept is based on rapidly increasing evidence indicating that a large variety of acquired human

diseases may, in fact, be due to genetic susceptibility. The data have, in large part, been derived from observations on the significant association between genes (and their products) within the major histocompatibility complex (MHC) on chromosome 6 and certain autoimmune or inflammatory disease states.[3] The enormous number of studies in this field have had to depend on technically demanding methods to assay gene products, including lymphocyte cytotoxicity with specific anti-HLA antisera, mixed leukocyte culture and B cell alloantigen detection using incompletely characterized, naturally occurring antisera.[4] Moreover, as new antisera become available and better gene product recognition becomes possible, old data are quickly outdated. Consequently, the reports of MHC-disease associations proceed at a breathtaking pace leaving all but the *insiders* awash in a sea of confusion and despair.

Nevertheless, the message to be drawn from these reported associations can be readily understood by all scientists interested in human chronic disease. The intriguing possibility exists that MHC genes, or their products, are responsible for the fertile soil—and the environment contains the seed(s). That this is the case in every other species studied is in little serious doubt. The science of immunogenetics has already yielded conclusive data on the existence of immune-response (that is, disease susceptibility) genes within the MHC of various subhuman species, necessary for the expression of certain forms of natural or experimental disease.[5] Circumstantial evidence that similar genes exist in humans continues to accumulate, although the pure-bred strains, well-identified antigenic stimulus and discrete immune response required for definitive proof continue to elude clinical investigators (and may always do so).[6] Nevertheless, a hypothesis linking MHC genes or their products with various forms of human autoimmune disease has gained widespread popularity.[7] In the case of the seronegative spondyloarthropathies, the association with HLA-B27 is so strong that a direct role of the genetically determined cell surface antigen has to be considered. Here, too, the necessary tools for investigation are lacking.

Assuming that certain types of rheumatic disease are genetically predetermined (notably, the seronegative spondyloarthropathies), what are the environmental triggers? Dr. Calin correctly indicates the suspicious presence of various enterobacteria and certain urethral organisms preceding or accompanying the Reiter syndrome and other types of *reactive* arthritis.[8-10] The potential role of these infectious agents in triggering a genetically controlled immune or autoimmune response that leads to connective tissue inflammation is unknown. But the possibilities are intriguing. Rheumatologists have not proved themselves very adroit as therapeutic masters of the in vivo inflammatory response. Perhaps we might shine a brighter light as purveyors of disease prophylaxis, either by excluding or avoiding environmental triggers or by interrupting or short-circuiting the aberrant (that is, pathogenic) immune response.

So it is that Dr. Calin's article may have two different and opposite impacts on readers. Some may feel a degree of despair at the apparent inevitability of certain types of chronic rheumatic disease. Conversely, the excitement at approaching disease prevention or control by manipulation of soil or seed at a preclinical phase should dispel all such gloom.

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REFERENCES

1. Proceedings on the Conference on Pseudogout and Pyrophosphate Metabolism. Arthritis Rheum 19:No 3 (Suppl) 1976
2. Wright V, Moll JMH: Seronegative Polyarthritis. New York, North-Holland Publishing Co, 1976
3. Bluestone R: Histocompatibility antigens and rheumatic diseases. Kalamazoo, MI, Scope Publications, The Upjohn Company, 1978
4. Bach FH, van Rood JJ: The major histocompatibility complex. N Engl J Med 295:806-813, 872-877, 927-936, Oct 7, 14, 21, 1976
5. Dietz MH, Bluestone R: The major histocompatibility complex and disease. J Chron Dis 31:307, 1978
6. Kemple K, Bluestone R: The major histocompatibility complex and rheumatic diseases. Pathobiol Ann 7:305, 1977
7. Reinertsen JL, Klippel JH, Johnson AH, et al: B-lymphocyte alloantigens associated with systemic lupus erythematosus. N Engl J Med 299:515-518, Sep 7, 1978
8. Ebringer RW, Cawdell DR, Cowling P, et al: Sequential studies in ankylosing spondylitis association with Klebsiella pneumoniae in disease. Ann Rheum Dis 37:1, 1978
9. Aho K, Ahvonen P, Lassus A, et al: HL-A 27 in reactive arthritis—A Study of Yersinia arthritis and Reiter's disease. Arthritis Rheum 17:521-526, Sep-Oct 1974
10. Holmes KK, Handsfield HH, Wang SP, et al: Etiology of nongonococcal urethritis. N Engl J Med 292:1199-1205, Jun 5, 1975

CASE REPORTS

Refer to: Patel R, Ansari A, Hughes JI: Myoglobinuric acute renal failure associated with phencyclidine abuse. West J Med 131:244-247, Sep 1979

Myoglobinuric Acute Renal Failure Associated With Phencyclidine Abuse

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PHENCYCLIDINE (also known as PCP, angel dust, crystal and hog) has become an important drug of abuse since it was first introduced as a street drug in San Francisco in 1967.[1] It is manufactured for use as an anesthetic in veterinary medicine but can be easily synthesized in a home laboratory from commercially available precursors. It is sold in a variety of physical forms and can be ingested, smoked, inhaled or injected. It is a frequent ingredient of other drugs of abuse, and in one survey was detected in 184 of 237 samples of illicit drugs.[2]

Phencyclidine is an analgesic which acts primarily on the central nervous system by stimulation or depression. In man, these effects are highly dose-dependent, and consist of some combination of schizophreniform psychosis, analgesia, anesthesia and sympathetic dysfunction.[3] Acute rhabdomyolysis and myoglobinuria not associated with renal dysfunction have recently been reported in association with phencyclidine abuse.[4] We are unaware of any reports of myoglobinuric acute renal failure developing in persons who abuse phencyclidine. Because of this, the following two cases in which phencyclidine toxicity was associated with myoglobinuric acute renal failure are of interest.

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Submitted, revised, February 8, 1979.

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Methods

Urine specimens were screened by Laboratory Procedures, Inc. (Woodland Hills, California) for the following groups of toxic substances: barbiturates, amphetamines, narcotics, hypnotics, analgesics, alcohol and phencyclidine. The initial screen was done using thin layer chromatography and positive results were confirmed by gas liquid chromatography.

Reports of Cases

CASE 1. A 25-year-old man was admitted to hospital in stupor four hours after smoking cigarettes sprinkled with phencyclidine. He was agitated and was placed in soft restraints to control the purposeless movements of his arms and legs. Blood pressure was 120/80 mm of mercury, pulse 120 per minute, temperature 38.1°C (100.6°F), respiration 18 per minute. Heart, lungs and abdomen were normal. Horizontal nystagmus was present but the remainder of the neurological findings were within normal limits.

Laboratory studies gave the following values: hematocrit was 39 percent; leukocyte count 13,200 per cu mm; serum sodium was 134, potassium 5.2, chloride 98 and bicarbonate 24 mEq per liter; blood urea nitrogen (BUN) was 13, serum creatinine 1.2, glucose 120 and calcium 9.2 mg per dl. Analysis of urine showed the following: specific gravity 1.016, pH 5.5, protein and glucose negative, 1 to 2 leukocytes and 0 to 1 red blood cell per high-power field, and no casts. The urine was positive for phencyclidine but negative for the other substances listed in the Methods section. An x-ray film of the chest and an electrocardiogram showed no abnormalities.

On the following day, BUN was 52 and serum creatinine 4.8 mg per dl. Analysis of urine showed specific gravity 1.007, pH 5.0, trace protein, glucose negative, 6 to 8 leukocytes and 1 to 2 red blood cells per high-power field, and numerous brown-stained granular casts. Spot urine sodium was 46 and potassium 18 mEq per liter. On the tenth day, BUN was 75 and serum creatinine 8.5 mg per dl, and a renal consultation was requested. On that day, serum creatine phosphokinase was 1,866, lactic dehydrogenase 694, glutamic oxaloacetic transaminase 441 and glu-

tamic pyruvic transaminase (SGOT) 89 IU per liter. Urine excreted on the same day was positive for myoglobin by the immunodiffusion technique. A diagnosis of myoglobinuric acute renal failure was made and the patient was treated conservatively. The serum creatinine level stabilized and declined on the 15th day. On the 26th day, the serum creatinine concentration was 1.3 mg per dl.

CASE 2. A 33-year-old man was brought to the hospital for abnormal behavior four hours after smoking two marijuana cigarettes laced with phencyclidine. He was evaluated by a psychiatrist who prescribed haloperidol. Urine specimens were taken for toxicology studies and the patient was discharged after overnight observation. Restlessness and agitation developed later that night, and he continued to "thrash about" periodically for the next two days; he was then readmitted to hospital. The patient had had to be physically restrained at home.

On admission, he complained of aching in the legs and of decreased urination. He was conscious, alert and orientated. Blood pressure was 162/98 mm of mercury, pulse 84 per minute, temperature 37°C (98.7°F) and respiration 16 per minute. The heart, lungs and abdomen were normal. The calf muscles were diffusely tender. Results of the neurological examination were within normal limits.

The following values were shown on laboratory studies: hematocrit was 42 percent; leukocyte count 10,000 per cu mm; serum sodium 131, chloride 95, potassium 5.6 and bicarbonate 17 mEq per liter; BUN 98, serum creatinine 13.8, calcium 5.7, phosphate 9.0, uric acid 15 and glucose 102 mg per dl. Analysis of urine showed specific gravity 1.008, pH 6.0, protein 1+, glucose 0, 2 to 3 leukocytes and 1 to 2 red blood cells per high-power field, 10 to 12 golden-brown coarsely granular casts per low-power field. On the next day, serum creatine phosphokinase was 2,900, SGOT 450, lactic dehydrogenase 800 and alkaline phosphatase 78 IU per liter. Urine specimens taken during the first but not the second admission were positive for phencyclidine but not for the other toxic substances listed in the Methods section. Myoglobin was detected by immunodiffusion in the second urine specimen. X-ray studies of the chest and an electrocardiogram showed no abnormalities.

Myoglobinuric acute renal failure was diagnosed and peritoneal dialysis was instituted. After 40 exchanges, BUN was 102 and serum creatinine 12.0 mg per dl. Thrice weekly hemodialysis was begun and continued for two weeks. On the 13th day, the serum calcium level rose to 12.9 mg per dl and, therefore, saline infusion and intravenous administration of furosemide were begun. The serum calcium value was normal six days later. Six weeks after the patient's admission, the serum creatinine level was 1.2 mg per dl.

Discussion

In the first patient, urinary abnormalities and rise in serum creatinine were first observed 24 hours after smoking phencyclidine. The second patient had severe renal failure by the time we saw him three days after he used the drug. The development of renal failure in these two patients in close temporal relationship to phencyclidine exposure suggests a causal relationship. We suspected myoglobinuria to be the cause of renal failure in our patients because neither was in shock and urine specimens from both contained pigmented granular casts and were toluidine-positive but free of significant hematuria. Our diagnoses were confirmed by the finding of elevated serum creatine phosphokinase and other muscle enzymes, and of myoglobin in specimens of urine.

The myoglobinuria was presumed to be secondary to acute rhabdomyolysis although muscle biopsies were not done in either of the patients. This result could have been due to a direct toxic effect of phencyclidine on the skeletal muscle or of excessive involuntary muscle activity. In the absence of any evidence for the former,[5] we favor the latter inference. A remote possibility is that myoglobinuria was caused by a reaction to some component drug contained in the phencyclidine used by our patients,[6] although none was detected by analysis of urine. Neither of our patients had a history of alcohol abuse and alcohol was not detected in urine specimens; therefore, acute alcoholic rhabdomyolysis was unlikely to have been the cause of myoglobinuria.

The mechanism leading to rhabdomyolysis and myoglobinuria in our patients is unclear. In both our patients, violent involuntary muscle activities necessitated the use of physical and mechanical restraints. Therefore, dystonic muscle activity was accompanied by isometric muscle contractions. This observation in patients may be relevant when considered in the light of the experimental observations of Kuncl and Meltzer[7] on the effect of phencyclidine in rats. They noted that injection

of phencyclidine in rats produced severely exaggerated locomotor activity. Pronounced rise in serum creatine phosphokinase was observed when phencyclidine-treated animals were restrained in cages. The serum enzyme level correlated with isometric muscle tension that developed when the animal was under restraints. Nonspecific myopathic changes consisting of scattered necrosis of muscle fibers and myofibrillar disruption were seen. These muscle changes did not occur when phencyclidine-treated animals similarly restrained had the motor nerve to the biopsied muscle area cut before the injection of the drug. Similarly, rhabdomyolysis did not occur in the restrained untreated, or in the unrestrained phencyclidine-treated animals. In support of these observations, Cogen and co-workers[4] have described a dramatic fall in the serum muscle creatine phosphokinase from a level of 40,000 to 9,000 units within 24 hours in a patient with phencyclidine toxicity in whom intentional peripheral motor nerve paralysis was induced with pancuronium. These findings suggest that in phencyclidine toxicity, rhabdomyolysis may be a consequence of vigorous muscle activity against restraint.

In our second patient, renal failure was initially treated with peritoneal dialysis. However, after 40 exchanges, there was remarkably little change in the serum creatinine concentration while the BUN actually rose. Subsequently, intensive hemodialysis was required to control the uremia. Nolph and associates[8] have described a similar experience in patients in whom acute renal failure develops in connection with heat stress and exercise, where the mechanism of renal failure is presumably identical. Therefore, in severe cases, the course of acute renal failure may resemble that in traumatic cases, and may require repeated hemodialysis. Nonetheless, complete recovery of renal function ensued in both our patients, an observation that agrees with the generally good prognosis reported by others[9] in cases of renal failure associated with nontraumatic rhabdomyolysis and myoglobinuria.

Transient hypercalcemia which complicates the recovery phase of myoglobinuric renal failure in approximately 20 percent to 25 percent of cases[10,11] did occur in our second patient. Meroney and associates[12] have shown in experiments with animals that acute renal failure facilitates calcium deposition in necrotic muscles. While the calcium content of traumatized muscles in dogs with intact kidneys doubled within six hours of injury, this increase was greater than tenfold after nephrectomy. These changes were not seen in the nontraumatized muscles. Clinically, radiologic and biochemical evidence of calcification involving the affected muscles has been reported in some patients during the oliguric phase of myoglobinuric renal failure.[9,10] More recently, using the more sensitive technetium-99-diphosphonate scan, Akmal and co-workers[11] were able to detect the presence of calcium deposits in the muscles of all four patients seen with acute renal failure associated with nontraumatic rhabdomyolysis. It has been suggested[11] that hypercalcemia that is seen in some cases during the recovery phase of myoglobinuric acute renal failure may be a consequence of remobilization of these calcium deposits from the damaged muscles into the extracellular space. There is evidence that the appearance of hypercalcemia may be related to the degree and severity of muscle damage and, therefore, the amount of calcium deposited in the injured tissues.[9]

We have been unable to find any report of frank renal failure associated with phencyclidine toxicity in the English language literature. However, in a recent article in French, Dandavino and associates[13] described the development of acute renal failure in an agitated, comatose patient suffering from phencyclidine toxicity. In this patient muscle enzyme values were elevated but a biopsy study of muscle showed no abnormalities. The renal failure was ascribed to a vasculitis and was treated with corticosteroids. It is possible that in their patient, as in ours, there was unrecognized myoglobinuric acute renal failure.

Use of phencyclidine as an illicit drug is becoming a serious problem. Cogen and associates[4] were the first to describe the occurrence of myoglobinuria in association with phencyclidine toxicity. To our knowledge, the two cases reported in our paper are the first in which myoglobinuric acute renal failure developed during the course of phencyclidine abuse. It is necessary that these potentially life-threatening complications of this drug when taken in excess be publicized. Physicians treating such cases should look for the development of myoglobinuria and acute renal failure in their patients.

Summary

Two cases of myoglobinuric acute renal failure associated with phencyclidine abuse are described. Phencyclidine intoxication should be included

among the growing list of causes of nontraumatic rhabdomyolysis and myoglobinuria.

REFERENCES

1. Rainey JM, Crowder MK: Prevalence of phencyclidine in street drug preparations. N Engl J Med 290:466-467, 1974
2. Hart JB, McChesney JC, Grief M: Composition of illicit drugs and the use of drug analysis and abuse abatement. J Psychedelic Drugs 5:83-88, 1972
3. Burns SR, Lerner SE, Corrado R, et al: Phencyclidine—States of acute intoxication and fatalities. West J Med 123:345-349, Nov 1975
4. Cogen FC, Rigg G, Simmons JL, et al: Phencyclidine-associated acute rhabdomyolysis. Ann Intern Med 88:210-212, 1978
5. Domino EF: Neurobiology of phencyclidine. Int Rev Neurobiol 6:303-347, 1964
6. Grossman RA, Hamilton RW, Morse BM, et al: Nontraumatic rhabdomyolysis and acute renal failure. N Engl J Med 291:807-811, 1964
7. Kuncl RW, Meltzer HY: Pathologic effect of phencyclidine and restraint on rat skeletal muscle: Prevention by prior denervation. Exp Neurol 45:387-402, 1974
8. Nolph KD, Whitcomb ME, Schrier RW: Mechanism for inefficient peritoneal dialysis in acute renal failure associated with heat stress and exercise. Ann Intern Med 71:317-326, 1969
9. Koffler A, Friedler RM, Massry SG: Acute renal failure due to non-traumatic rhabdomyolysis. Ann Intern Med 85:23-28, 1976
10. Patel R, Ford J: Hypercalcemia in acute renal failure. NZ Med J 84:482-483, 1976
11. Akmal M, Goldstein DA, Telfer N, et al: Resolution of muscle calcification in rhabdomyolysis and acute renal failure. Ann Intern Med 89:928-930, 1978
12. Meroney WH, Arney GK, Segar WE, et al: The acute calcification of traumatized muscle with particular reference to acute post-traumatic renal insufficiency. J Clin Invest 36:825-832, 1957
13. Dandavino R, Friborg J, Beudry C, et al: Un cas d'intoxication aigue a la phencyclidine avec atteinte musculaire important et insufficiance renale aigue. Union Med Can 104:57-60, 1975

Refer to: Edwards JE Jr, Combs WA, Guze LB: Malignant pseudomonas external otitis. West J Med 131:247-250, Sep 1979

Malignant Pseudomonas External Otitis

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MALIGNANT PSEUDOMONAS EXTERNAL OTITIS is a severe, necrotizing, external ear canal infection most often occurring in elderly persons with diabetes mellitus. It is accompanied by high complication and mortality rates.[1] Early diagnosis and therapy can circumvent the complications of cranial nerve palsies, osteomyelitis of the skull, meningitis, parotitis, vascular thrombosis, septicemia and death. A primary care physician usually first sees a patient with the disease but, because of few descriptions of the disorder in the general medical literature,[2-5] he may not be completely familiar with the presentation and complications. Therefore, we report the case of a patient who was cured without complications by parenteral administration of antibiotics and appropriate surgical therapy. The literature also is reviewed.

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Submitted January 2, 1979.

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Report of a Case

The patient, a 70-year-old white man, had been treated uneventfully for diabetes mellitus with chlorpropamide for four years. One week before admittance to hospital, the patient presented to a general medical clinic with pain in both ears. Treatment was begun with local administration of drops (polymyxin B, bacitracin, neomycin, hydrocortisone) and orally given phenoxymethyl penicillin for bilateral external otitis. The pain in the right ear resolved but a painful purulent discharge continued from the left ear. Despite wick packings and topical therapy with antibiotics (colistin, neomycin, thonzoniumbromide, hydrocortisone), the condition progressed to ulceration of the floor of the left external canal. This condition was accompanied by a small polypoid mass with the gross appearance of granulation tissue. Pure cultures of Pseudomonas aeruginosa were obtained twice. A biopsy specimen of the polypoid mass showed granulation tissue with no evidence of malignancy. Because of the unresponsiveness of the lesion to treatment, the culture results and the history of diabetes, the patient was admitted to hospital with a diagnosis of malignant Pseudomonas otitis externa so that parenteral administration of antibiotics could be begun.

On admission an ulcer was noted on the floor of the canal of the left ear at the juncture of the membranous and cartilaginous portions and there was purulent discharge and pronounced tenderness over the mastoid. An audiogram documented a mild, left sensorineural hearing loss at 2,000 to 8,000 Hz. Findings on x-ray studies of the mastoid showed slight clouding. Probing of the ear dis-

closed a deep sinus tract that extended at the junction of the membranous and osseous portion of the external canal back to the still intact, bony roof of the mastoid. Chondritis was present to the level of the mastoid roof.

A regimen of gentamicin was begun, 70 mg given intramuscularly three times a day, and gentamicin otic drops. Because there was no improvement, administration of carbenicillin, 24 grams per day, was begun 13 days after the gentamicin was given. Following a ten-day course of carbenicillin and a 26-day course of gentamicin, the lesion healed. However, four days following discontinuation of the antibiotics, the purulent left ear drainage recurred. Pseudomonas aeruginosa was cultured again; repeat x-ray studies of the mastoid showed improved aeration compared with findings on the previous studies. Intramuscular administration of gentamicin, 70 mg per kg of body weight per day, and intravenous therapy with carbenicillin 30 grams per day, were reinstituted. Five days later extensive debridement of the entire external canal was carried out. No bone involvement was found. Gentamicin drops were given locally and there was gradual and uneventful wound healing. There were no recurrences, middle ear involvement or cranial nerve palsies. Cultures for acid-fast bacilli and fungi were all negative.

Discussion

There are two distinctly different ways in which Pseudomonas infects the external ear canal. The most common condition, frequently referred to as swimmers' ear or simple external otitis, is a mild infection, usually seen in children. It responds to local therapy without sequelae. This relatively benign form of external otitis should be clearly differentiated from malignant Pseudomonas external otitis which occurs primarily in elderly diabetic patients and is associated with multiple complications including hearing loss, cranial nerve palsies, parotitis, osteomyelitis, intracranial vascular thrombosis, meningitis, septicemia and, in a high percentage of patients, death. The first description of this process was in 1959.[6] Since then experience with approximately 127 cases has been described in the English language literature[1-25] and several additional cases have been reported in the foreign literature. Chandler, who originally coined the term malignant Pseudomonas external otitis in 1968,[1] has had the largest single experience with the disorder. In 1977 he updated his observations, while describing in detail the complications of sigmoid sinus thrombosis and secondary mastoiditis.[24] With the exception of four instances,[2-5] all reports of this disease have been published in the ear, nose and throat, and the neurological literature.

Except for 15, all of the 127 cases have involved patients with some form of diabetes, ranging from mild abnormalities of glucose tolerance to overt, insulin requiring disease. The ages of the patients have ranged from 7 months to 91 years (with an average age of 70 years). A sex or race ratio cannot be determined accurately, although it appears that Caucasians have predominated.

At first the infection is relatively inconspicuous. Gradually it worsens, and a painful, purulent discharge from the external canal develops. Occasionally, minor trauma has precipitated the infection. One case, for example, was associated with trauma from a hearing aid and one with lancing of an external canal furuncle.[1] Another occurred "after removal of a piece of hard wax with some flesh attached."[11] Except for those three instances, no specific initiating event or clinical circumstance has been defined.

After the process becomes established its appearance is so characteristic that it deserves special comment. The purulent drainage is associated with a polypoid mass of granulation tissue at the juncture of the membranous and osseous portion of the external canal. Accompanying findings have been mastoid tenderness, stenosis of the external canal, periauricular cellulitis, contiguous involvement of the tympanic membrane and hearing loss.

Kim,[9] in his review of x-ray findings in this disorder, pointed out the value of ear tomograms to assess the extent of involvement of the initial process. Early features of extension to bone included clouding of the middle ear cavity, destruction of the lateral attic wall, and destruction and dislocation of the ossicular structures. In late stages destruction of the tegmen and jugular foramen and extension to the petrous apex were shown on x-ray films.

Three directions of extension from the original external canal site have been reported: (1) toward the middle ear, (2) inferiorly and posteriorly into the mastoid air cells and (3) anteriorly into the parotid gland and tempromandibular joint. Ultimately, in many cases infection extends into the intracranial cavity. Associated with this

extension from the external canal focus has been a high incidence of cranial nerve palsies; the facial nerve is most frequently affected by extracranial encroachment at the stylomastoid foramen.

Dinapoli and Thomas[2] in their review of the neurological complications noted that the 7th, 10th, 11th, and 12th cranial nerves were the most frequently involved early in the disease's course in their patients. In contrast, the nerves involved later were the 3rd, 5th and 6th. Involvement of the 10th, 11th and 12th was a complication of osteomyelitis at the base of the skull near the jugular and hypoglossal foramina. The involvement of the 3rd, 5th and 6th cranial nerves was considered to be a result of progressive osteomyelitis, but concurrent meningitis or spread through the internal carotid artery and its branches could not be ruled out. Although multiple cranial nerve involvement is generally associated with a poor prognosis, in one report a patient with multiple palsies survived with only minimal residua.[18]

In Chandler's 1977 report, he reviewed his experience with this external ear disease in 72 patients.[24] He emphasized the reduction of morbidity and mortality that has accompanied an increased awareness of the potential seriousness of the infection, the institution of carbenicillin and gentamicin therapy, and an increased surgical aggressiveness when appropriately indicated during failure of medical treatment. In addition, he expanded the literature on the complication of sigmoid sinus thrombosis by describing four cases of proven thrombosis and another seven of suspected thrombosis. Although in most of these cases there was clinical involvement of the nerves leaving the jugular foramen, in one patient sigmoid sinus thrombosis was shown during surgical operation and there were no cranial nerve deficits. In addition, in this review, Chandler pointed out the complication of mastoiditis without middle ear involvement and suggested that whenever the diagnosis of malignant Pseudomonas external otitis is made a series of x-ray studies of the mastoid should be done early. He described several cases of mastoid involvement which responded to carbenicillin and gentamicin therapy, making surgical drainage unnecessary.

A relatively clearly defined approach to patients with malignant Pseudomonas external otitis can be developed from a review of the literature. The initial therapy should consist of topical administration of antibiotics (gentamicin wick packing). If response is not rapid, local debridement should be undertaken and the diagnosis of malignant Pseudomonas external otitis considered if cultures are positive for Pseudomonas. Cultures of the granulation tissue with full sensitivities of the organism should be done because of an emerging resistance of Pseudomonas to gentamicin. If improvement does not occur, intravenous administration of carbenicillin and gentamicin should be instituted. Although the experience is limited, tobramycin[19] or amikacin should be an acceptable alternative to the gentamicin; ticarcillin[19] should be an acceptable substitute for the carbenicillin. If the response is less than optimal, appropriate surgical debridement should be undertaken. Early diagnosis and parenteral administration of antibiotics, combined with appropriate surgical therapy, are necessary for minimizing disfiguring and potentially fatal complications.

Summary

Since 1959, when the first case of malignant Pseudomonas external otitis was described, approximately 127 cases have been reported in the English language literature. Diabetes has been present in 88 percent of the patients. The average age has been 70 years.

A typical presentation includes a chronically infected external ear canal with Pseudomonas grown on culture and no response to topical treatments. A polypoid mass of granulation tissue has been found frequently at the juncture of the cartilagenous and membranous portion of the canal. The infection may progress downward or medially from its external canal origin and cause the complications of cranial nerve palsies (32 percent of Chandler's patients had facial nerve palsy), osteomyelitis of the skull, meningitis, parotitis, sigmoid sinus thrombosis, septicemia and death. The overall mortality has been 33 percent. Tomograms of the middle ear area may be helpful in showing if extension to bone, the mastoid sinuses or the middle ear has occurred.

Current suggestions regarding management include (1) early diagnosis whenever possible (determining extension of infection beyond the confines of the external canal), (2) early use of parenterally given carbenicillin and gentamicin if local measures are of no benefit (antibiotic alternatives include ticarcillin instead of carbenicillin and tobramycin or amikacin instead of gentamicin) and (3) early surgical debridement

if there is no improvement after the parenteral administration of antibiotics.

REFERENCES

1. Chandler JR: Malignant external otitis. Laryngoscope 78: 1257-1294, Aug 1968
2. Dinapoli RP Thomas JE: Neurologic aspects of malignant external otitis: Report of three cases. Mayo Clin Proc 46:339-344, May 1971
3. Caruso VG, Griffiths CM, Bailey BJ: Malignant external otitis. Tex Med 73:106-133, May 1977
4. Mitchell C, Weston M, Parsons V, et al: "Malignant" otitis externa in a patient on haemodialysis. Br J Clin Pract 29:126-127, May 1975
5. Zaky DA, Bentley DW, Lowy K, et al: Malignant external otitis: A severe form of otitis in diabetic patients. Am J Med 61: 298-302, Aug 1976
6. Meltzer PE, Kelemen G: Pyocyaneous osteomyelitis of the temporal bone, mandible and zygoma. Laryngoscope 69:1300-1316, Oct 1959
7. Morgenstein KM, Seung HI: Pseudomonas mastoiditis. Laryngoscope 81:200-215, Feb 1971
8. Wilson DF, Pulec JL, Linthicum FH Jr: Malignant external otitis. Arch Otolaryng 93:419-422, Apr 1971
9. Kim BH: Roentgenographic findings of malignant external otitis. Am J Roentgenol Radium Ther Nucl Med 112:366-372, Jun 1971
10. Shanon E, Bialystock G, Schujman E, et al: Pseudomonal granulomatous external otitis. Acta Otolaryng 73:374-378, Apr 1972
11. Schwarz G, Blumenkrantz M, Sundmaker W: Neurologic complications of malignant external otitis. Neurology 21:1077-1084, Nov 1971
12. Chandler JR: Pathogenesis and treatment of facial paralysis due to malignant external otitis. Ann Otol 81:648-658, Oct 1972
13. Evans ITG, Richards SH: Malignant (necrotizing) otitis externa. J Laryngol Otol 87:13-20, Jan 1973
14. Aldous EW, Shinn JB: Far advanced malignant external otitis: Report of a survival. Laryngoscope 83:1810-1815, Nov 1973
15. Cohn AM: Progressive necrotizing otitis—Malignant external otitis. Arch Otolaryngol 99:136-139, Feb 1974
16. Petrozzi JW, Warthan TL: Malignant external otitis. Arch Dermatol 110:258-260, Aug 1974
17. Chandler JR: Malignant external otitis and facial paralysis. Otolaryngol Clin North Am 7:375-383, Jun 1974
18. Faden A: Neurological sequelae of malignant external otitis. Arch Neurol 32:204-205, Mar 1975
19. Prasad U: Malignant external otitis. Laryngol Rhingol Otol 90:963-965, Oct 1976
20. Horwitz MJ, Templeton TP: Progressive necrotizing external otitis: Treatment with ticarcillin and tobramycin. Laryngoscope 87:1836-1840, Nov 1977
21. Pace-Balzan J: Necrotizing otitis externa. J Laryngol Otol 91:735-738, Aug 1977
22. Joachims HZ: Malignant external otitis in children. Arch Otolaryngol 102:236-237, Apr 1976
23. Meyerhoff WL, Gates GA, Montalbo PJ: Pseudomonas mastoiditis. Laryngoscope 87:483-492, Apr 1977
24. Chandler JR: Malignant external otitis: Further considerations. Ann Otol 86:417-428, Jul 1977
25. John AC, Hopkin NB An unusual case of necrotizing otitis externa. J Laryngol Otol 92:259-264, Mar 1978

Identifying the Gilbert Syndrome

REDUCED ACTIVITY of the enzyme responsible for conjugation of bilirubin is encountered in the very uncommon Crigler-Najjar syndrome and it is also encountered in the much more common Gilbert syndrome, probably the commonest cause of jaundice that you will encounter in your clinical practices. It occurs in something like 5 percent of the population and it is identified by demonstrating that the isolated increase in bilirubin seen on an SMA-12 is due to an unconjugated hyperbilirubinemia and not a direct hyperbilirubinemia. I had a patient referred to me yesterday who had been followed for six months as a case of hepatitis because they had failed to do the fractionation of a bilirubin and identify that it was an unconjugated hyperbilirubinemia present. So Gilbert syndrome is very common and needs to be identified because it is an entirely benign condition that requires no specific treatment.

—MARTIN BLACK, MD, *Philadelphia*

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Techniques in Treatment of Retained Gallstones

TO THE EDITOR: In his letter in the August issue, Howard A. Shapiro, MD, mentions my Editorial Comment[1] that appeared in the May 1979 issue. I am delighted to hear that an expert like Dr. Shapiro has been able to carry out 5 sphincterotomies for common bile duct stone extraction and 45 others with no deaths and only two complications. Dr. Zimmon (David S. Zimmon, MD, New York University School of Medicine, personal communication, 1979) has recently surveyed the Endoscopy Society and found that 690 sphincterotomies were carried out in 752 attempts. While both of these authors confirm the 95 percent success rate found in 2,304 papillotomies carried out in Europe, this technique has only been done for less than three years in the United States and then by fewer than ten persons (according to Dr. Zimmon).

I feel that this approach should be evaluated like any other surgical procedure. Many operations such as transduodenal sphincterotomy, thoracoabdominal splanchnicectomy for hypertension and the Vineberg operation for angina were enthusiastically supported at first, only to be later abandoned. This is a difficult procedure which cannot be easily carried out by every endoscopist. I doubt that other endoscopists less skilled than Drs. Shapiro and Zimmon will be able to carry out these procedures with the same low morbidity and mortality rate. For these reasons I feel that this procedure deserves further evaluation before being removed from the status of an experimental one. We as surgeons are required to do this in our cases. Only five such cases have been carried out by three physicians in Seattle. We feel that a double-blind series such as advocated by Blumgart[2] would be useful and that it should be carried out over a long period of time.

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REFERENCES

1. White TT: Techniques in treatment of retained gallstones (Editorial Comment). West J Med 130:435-437, 1979
2. Blumgart LH, Wood CB: Endoscopic treatment of biliary-tract diseases. Lancet 2:1249, 1978

Another View of Functional Overlay

TO THE EDITOR: In his article in June (Bromberg W: Functional overlay: An illegitimate diagnosis? West J Med 130:561-565, 1979), Dr. Walter Bromberg has strained mightily in order to give extended meaning and deeper significance to the expression *functional overlay*. This phrase is usually no more than an offhand notation of physicians who are unacquainted with the perplexities of psychiatry—and wish to leave it that way—or with the true motives of their patients, or perhaps do not intend to judge them. Functional overlay is hence intentionally ambiguous and empty as are its analogues: emotional overtones, functional superimposition or emotional shock. The term does not deserve the heavy-handed treatment accorded to it in the article nor the attempt to create a niche for it in the spectrum that lies between malingering at one extreme and inchoate hysteria at the other.

As I see it, there is no need to formalize functional overlay, although Bromberg asserts that "the concept has concrete meaning in medicolegal areas." By that, I take him to mean that the concept has proved useful to attorneys in obtaining cash awards. Bromberg's analysis suggests that functional overlay should be inserted as a recognizable psycho-entity which includes preconscious, unconscious and psychophysiological elements but excludes resentment, revenge and rapacity. By this means the influences of free will or choice are bypassed by this schema which places func-

tional overlay close to hysteria but far removed from imposture and malingering. Such an artificial structure of psychical operations will undoubtedly be useful to claims lawyers all of whom plead that their clients are victims of unknown and uncontrollable psychic forces released by an accident. In this respect Bromberg's argument fills the bill.

Is such a formulation true? Charcot[1] (1825 to 1893) had the following to say:

> This brings me to say a few words about malingering. It is found in every phase of hysteria and one is surprised at times to admire the ruse, the sagacity, and the unyielding tenacity that especially the women, who are under the influence of a severe neurosis, display in order to deceive . . . especially when the victim of the deceit happens to be a physician.

Apropos to physicians and lawyers, he said,

> Indeed, everyone is aware that the human need to tell lies, whether for no reason at all than the practice of a sort of cult like art for art's sake or in order to create an impression, to arouse pity, etc., is a common event, and this is particularly true in hysteria.

In short, postaccident neuroses are not so devoid of self-perception and self-awareness that deception can be discounted. Bromberg's effort to establish another abstraction and call it functional overlay is inconsistent with long clinical observation and is unnecessarily complicating.

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REFERENCE

1. Guillain G: JM Charcot, 1825-1893—His Life and His Works, (Edited and Translated by Pearce Bailey). New York, Paul B. Hoeber, Inc, 1959, pp 138-139

Organized Medicine as 'My Doctors'

To the Editor: The editorial entitled "Organized Medicine as 'My Doctors' " in the May 1979 issue succinctly points out a malady that disturbs the present-day practice of medicine and appropriately recommends a potentially effective remedy. It can be hoped that individual members of the profession will respond and "try to make the doctor-patient relationship come alive . . . ." Recognizing and delineating the problem is the first important step. As pointed out, the terms *organized medicine* and *society* are impersonal designations that fail to indicate that each consists of many persons who have strong personal feelings and desires.

Taking a broad perspective of the development of the difficult circumstances that are evident between the profession and society demonstrates that there are many factors that have contributed to the unhappy situation. Among these there are some that the profession may have been in part responsible for and are, therefore, factors that might be improved. Doctors are sensitive people and the development of what is termed *defensive medicine* in response to pressures exerted by society is understandable even if regrettable. But, placing emphasis on the individual and his conduct of practice, especially that in maintaining the best in doctor-patient relationship, can be beneficial both for organized medicine and for society: And . . . "the millions of doctor-patient contacts that occur in America each day can be used to bring the message home."

In the context of delineating the factors that contribute to the malady and in seeking ways and means for gaining improvement, medical education from the first year in medical school through the years of hospital training carries a heavy responsibility. Scientific medicine (despite the remarkable advances, the massive increase in medical technologies and their usefulness) and the involvements of government and third party insurers (despite the necessity of each) are factors that tend to depersonalize and dehumanize the practice of medicine. Doctors are partially the products of their education, training and experience. Their genuine, native and fundamental idealism for rendering service to those who are ill should be preserved. Medical educators, especially those in clinical fields, should direct academic attention to the importance of maintaining personal relationships between doctors and patients. Medical education should acknowledge that the practice of medicine at its best remains an art, and is not a science. Although stated early in this century and before the influence of scientific medicine on medical education, the words of Sir William Osler are still pertinent. He advised that "It is much more important to know what sort of patient has a disease than what sort of disease a patient has" (*Aequanimitas and Other Lectures,* New York, 1914). And, in the matter of gaining knowledge and experience, students and trainees in medicine should acknowledge their individual responsibility to hold on to the basic idealism for service that leads most of them into the profession. With effort on the part of us all, there is reason to believe that the malady can be properly treated.

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An Incorrect Reference

To the Editor: While browsing through the July 1979 issue of the journal I came upon the section titled "Important Advances in Clinical Medicine," which outlined "Epitomes of Progress —Chest Diseases." The epitome "Weaning Criteria for Patients on Mechanical Respiratory Assistance" was of special interest, since I spent part of my internship at Loma Linda University Medical Center with Dr. John E. Hodgkin, who was at that time very interested in developing some objective criteria for weaning respirator patients.

The landmark article by Dr. Hodgkin, his colleague Dr. George Burton, and Michael Bowser, cited in the references, somehow received an incorrect title. This article did in fact appear in the March-April 1974 issue (Vol. 2, No. 2) of *Critical Care Medicine,* under the title "Respirator weaning." The title cited, "Variation in the occurrence of extracellular diffusible antigens in temperature induced variants of Erwinia herbicola Y46, and observation of their relationships with Erwinia amylovora," appeared in the *Canadian Journal of Microbiology* (Vol. 20, No. 5, pages 643-648), and deals with the possible relationship of E. herbicola to "fire-blight" affecting apple and pear trees.

As indicated in the original article and in the epitome, these criteria are not absolute predictors, and patients must be carefully monitored during the weaning process. However, a simple trial "off the respirator" without regard for the clinical and physiological factors outlined is no longer acceptable.

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Dr. Vernon is correct. The error, however, can be traced to the 1974 edition of the Cumulated Index Medicus *(Vol 15, page 1744).*

—Ed.

WSMA 90th Annual Meeting
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Special Session

PROFESSIONAL LIABILITY RISK MANAGEMENT
1:30 p.m., October 4

A proposal to help control malpractice claims, improve patient care and favorably influence insurance premiums.

- Mr. Oli Patrell
  Vice President, Aetna Life and Casualty, Hartford, Connecticut
  An overview of the Washington risk management partnership between WSMA and Aetna

- William O. Robertson, MD
  WSMA Past President; Member, WSMA-Aetna Negotiating Committee, Seattle
  Components of and process to implement a risk management program

- David K. Heaps, MD
  Chairman, WSMA Professional Liability Committee, Bellingham
  Report on findings of causative and correlative factors leading to allegations of malpractice in Washington

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- **Year of the Child**
- **Tuberculosis in Children: 1979**
- **Chronic Lung Disease in Children**

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- **Clinical Application of Abdominal Ultrasonography, C.T. and Nuclear Medicine**
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Information

Generic Screening

A Systems Approach to Patient Care Audit Studies

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RECENTLY, students of the audit process have questioned the value of continuing audit programs in their traditional format and have suggested exploring new directions and expansion of the scope for this process. Reports have substantiated that audits using the time-tested diagnosis and procedure methods of topic selection have not produced high yields of potential problems for analysis. Moreover, there seems to have been a lessening of professional satisfaction and educational value to be derived from the diagnosis and procedure oriented audits.

A new approach to patient care audits came about as an unexpected outcome of a study—the Medical Insurance Feasibility Study (MIFS)—jointly sponsored by The California Medical Association and The California Hospital Association. The study, designed and conducted by Don Harper Mills, MD, JD, Los Angeles; John S. Boyden, Jr., MD, LLB, Salt Lake City, and David S. Rubsamen, MD, LLB, Berkeley, was published in 1977.[1] It sought to identify potentially compensible events occurring in hospitals. An important by-product of this approach has been a new method of detecting patient care problems suitable for study by patient care audits. The name that has been given to this is *generic screening*.

A generic screen is a patient condition or a patient care event that might signal one or more problems in the health care system. For example, serious injuries are not expected to happen to patients in hospital. Should such an event occur it can be studied with the objective of preventing recurrence in the future. Generic screens provide new topics for audits, but most important they shift emphasis from merely assessing the care provided by health professionals to evaluating the entire system of care in an institution. After supervising and conducting many audits, one of our collaborators concluded that

> Gaps in patient care between what is desired and what actually occurs can only be identified in 15 percent of the audits performed in the traditional manner by looking at the performance of health care professionals in isolation. Eighty-five percent of these gaps can indeed be surfaced by an approach involving the "system" of patient care delivery. This "systems" evaluation technique calls for the inclusion of such factors as risk management events, exceptional patient care occurrences, scheduling deficiencies, policies, clinical data printouts, discharging planning, etc. *The addition of the generic-screening-generated audits which focus on problems in patient care would attain an almost 100 percent record in achieving "desired" care* (personal communication from Stanley A. Skillicorn, MD).

Examples of exceptional patient care occurrences that could lead to the development of generic screens are the following: patient sensitivity reactions to drugs, infections incurred in a hospital, more than one operating-room visit during a single hospital admission, unplanned repair of an organ during an operative procedure, neurologic deficit not present at admission, a patient who is febrile on discharge, or unplanned readmission for complications developing from a previous hospital admission.

The generic screening procedure begins with the selection of a potential problem or a generic criterion. This might be hospital-incurred trauma, for example. A screening level is then set, which in this instance might be 0 percent, that would require a review of all cases of patients incurring such an injury over a specified period of time. Instructions to the medical records department might stipulate exceptions, such as eliminating review of records in cases resolved before discharge or not requiring extended length of stay. Instructions for this generic screening criterion might be stated in this way:

- *Criterion*—hospital-incurred trauma,
- *Screening Level*—0 percent,
- *Exceptions*—problems resolved before discharge without increase in length of stay.

The medical records department would then be

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instructed to retrieve and review charts for patients who had had inhospital fractures, burns, lacerations requiring sutures, damage to teeth or other disabilities. Such minor problems as phlebitis or hematoma caused by infiltrated intravenous infusions and falls resulting only in bruises or simple lacerations not requiring sutures can be omitted. With this method, records to be reviewed will represent major injuries, problems needing attention.

Sources of generic screens may be any of the following: incident reports, infection control departments, medical care evaluation committees, medical record committees, utilization review, in-service training and education programs, clinical data printouts, health care provider complaints, patient dissatisfactions, hospital administrative issues, product review committees, liability claims, coronary care and resuscitation committees, safety committees, pharmacy committees and even social service department reports.

Following are three case studies to illustrate how generic screening criteria and subsequent audits can focus on problems and their causes. Each case study proceeds from a clinical suspicion to application of generic screening criteria to development of generic audit objectives. From that point, options include the development of generic criteria or suggestions for further generic audit studies.

Case Studies

CASE 1. The resident physician assigned to hospital admissions reported to the chief of staff that certain patients were being repeatedly admitted about every three to four months. This *revolving-door* syndrome is disturbing to both house staff and attending staff and exacerbates an increasingly tight bed situation. The audit committee was instructed to screen the problem.

The generic screen selected was frequent readmissions for the same diagnosis. Sources of information were the medical records department, clinical data printouts and utilization review committee reports.

In this example, 64 cases were discovered that required one or more readmissions during two years. These fell into three diagnostic categories: (1) acute pancreatitis or relapsing pancreatitis with associated conditions of chronic alcoholism or biliary calculi, (2) adult onset diabetes (insulin dependent) and (3) attempted suicide. A potential audit topic was chosen, which was the same as the generic screen—repeated hospital admission for the same diagnosis. The objectives of the audit were established: to evaluate causes of the revolving-door syndrome and to reduce its incidence. The suggested criterion used in the chart search was the presence or absence of notation regarding remedial programs to reverse causative factors.

CASE 2. The surgical review committee is reviewing the use of surgical suture material in view of technological and product improvements and reports of increased incidence of wound disruption requiring return to surgery. Before deciding on changes in suture materials or wound closure protocols, an extensive review of the surgical department's experience was recommended.

The generic screen selected was abdominal wound dehiscence. Sources of information were surgical logs and complication reports. In this example 15 such events were discovered during a two-year period in the departments of general surgery and gynecology.

Potential audit studies selected were the use of nonabsorbable sutures in clean-wound closure, delayed closure of wound in infected cases, use of drains in cases of potential infection and review of all types of wound closure in abdominal operations.

CASE 3. The pathology department reported to the chief of pediatrics that the percentage of high bilirubin levels in newborn babies exceeds the established standard of 10 percent of the nursery population. Whether these high levels were due to prematurity, physiologic causes or incompatibility was not an immediate concern. What concerned the department was the requirement that physicians borrow equipment from other hospitals in order to administer phototherapy.

The generic screen was unexplained hyperbilirubinemia in the newborn nursery. Sources of information were clinical data printouts, pathology laboratory reports and pediatric department standards for normal incidence of newborn jaundice. (In this example, a two-year study showed that 50 percent of babies in the newborn nursery had hyperbilirubinemia.)

Potential audit studies dealt with the influence of environmental factors in the hospital nursery (cleansing chemicals, for example) in causing hyperbilirubinemia in newborn babies and the

impact of prophylactic use of vitamin K for prevention of hyperbilirubinemia in newborns.

The completed audit showed that the prophylactic use of vitamin K had no impact on prevention of hyperbilirubinemia, but found that improvement was due to changing cleansing chemicals used in the nursery.

The benefit of generic screens is that they are nonspecific and may be applied to all patient records so that potential problems can be recognized and subjected to in-depth analysis using conventional audit techniques. Generic screens are objective rather than subjective and therefore they are not completely dependent upon documentation by a physician or nurse. They may be applied retrospectively, concurrently or prospectively, and they have the advantage of meeting demands for increased quality assurance activity without increasing the time demands upon physicians. Generic screens are readily adaptable to continual analysis by either manual or computer methods.

Summary

Generic screening is an effective way to monitor exceptional events for the purpose of identifying potential patient care problems upon which to focus audit studies. One of the objectives of the generic screening concept in the audit process is to isolate for an audit committee the problem areas in the delivery of patient care. The audit procedure is a performance evaluation system, not a *research* mechanism where absolute certainty is essential. All that is necessary for valid generic screening is probability, not certainty.

It is gratifying to note that many nationally prominent leaders in patient care evaluation have incorporated generic screening in their evaluation, risk management and patient protection programs.

REFERENCE

1. Mills DH (Ed): Report on the Medical Insurance Feasibility Study—Sponsored jointly by the California Medical Association and the California Hospital Association, 1977. San Francisco, Sutter Publications, Inc, 1977

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Information

Tamoxifen in the Management of Metastatic Cancer of the Breast

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TAMOXIFEN is a synthetic triphenylethylene derivative that exhibits potent antiestrogenic activity in several mammalian species.[1] It acts by inhibiting the binding of estradiol to a cytoplasmic receptor complex from normal endometrium and in adenocarcinoma of the breast and uterus.[2,3] The drug has undergone clinical studies in the United States after earlier trials in Europe and Great Britain[4,6] had shown an objective tumor regression in 25 percent to 40 percent of patients with metastatic breast cancer. This report will present the results of a clinical study using tamoxifen in 30 patients with stage IV breast carcinoma which was conducted at the Eisenhower Medical Center, Rancho Mirage, California, during the past two years. Since two patients are still receiving the drug, this communication is to some degree still preliminary.

Methods

After informed consent was obtained, women with advanced cancer of the breast and disease that could be evaluated were selected to receive tamoxifen. All were expected to survive at least six months so that a failure with the drug would not jeopardize the success of further hormonal manipulation. While the majority of women had lesions involving multiple sites, dominant areas of disease could nonetheless be identified. As is traditional, the cases were assigned to soft tissue, osseous and visceral dominant disease categories. All patients were postmenopausal either as a result of surgical ablation or by natural occurrence. Their ages ranged from 35 to 85 years,

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the mean age of 63 years being somewhat higher than in most series. Of the patients, 29 were white and one was Asian.

Patients were evaluated before tamoxifen therapy was begun and at one to three month intervals by physician interviews, physical examinations, complete blood counts, analyses of urine, serum calcium determinations, renal and hepatic chemistries, chest and skeletal roentgenograms, and bone scintiscans.

Two dose schedules, either 10 mg or 20 mg twice a day, of tamoxifen were used in a nonrandomized fashion. Treatment was designed to be given for 16 weeks, which is twice the average clinical doubling time of breast cancer, or until there was evidence of drug toxicity or progressive disease. It was considered possible to evaluate disease in patients if four weeks of treatment were completed. The following evaluative classifications were used:

- Complete response (CR). This classification included complete disappearance of all objective evidence of disease as indicated by findings on laboratory tests and x-ray studies of all involved sites with no evidence of clinical progression and with radiographic evidence of recalcification osteolytic lesions.
- Partial response (PR). This category included a 50 percent or greater decrease in the product of the two largest perpendicular diameters of measurable lesions with partial recalcification of osteolytic lesions and regression or no change in osteolytic lesions, with no appearance of new lesions or evidence of clinical progression.
- No change (NC). This category included a decrease of less than 50 percent or an increase of

TABLE 1.—*Patient Characteristics and Responses to Tamoxifen Therapy*

Patient	*Age*	*Disease Sites*	*Previous Therapy*	*Treatment Duration (Days)*	*Response*
Osseous Dominant					
1	53	Bone	S	736	PR
2	35	Bone, lung	S, RT, Ox, CT	37	P
3	76	Bone	S, RT, C	125	NC
4	70	Bone	S, E	112	NC
5	71	Bone	S	202	PR
6	68	Bone	S	440	PR
7	71	Bone, dura	S, RT, E, A	33	P
8	40	Bone, pleura	S, Ox, A	Drug withdrawn	
9	61	Bone, skin	S, E, A	201	PR
10	66	Bone, liver	S, RT	410	PR
11	85	Bone	S	120	NC
12	61	Bone, pleura	S, RT	350	PR
13	65	Bone, liver	S, HPx	260	PR
14	63	Bone	S, E, A	181	NC
15	66	Bone	S, RT, E, A	405	NC
16	52	Bone	S, RT, E	Drug withdrawn	
17	68	Bone	S, RT, E	765+	PR
18	61	Bone	S, RT, E A	75	P
19	44	Bone, liver	S, RT, Ox, CT	125	NC
Soft Tissue Dominant					
20	56	Skin, bone	S, RT, Ox, HPx	449	PR
21	63	Skin	S, RT, E, CT	491	PR
22	70	Soft tissue	S, E, A	35	P
Visceral Dominant					
23	70	Pleura, lung, bone	S, RT, CT	260	NC
24	42	Lung, bone	S, Ox, E, A, PR	58	P
25	71	Lung, soft tissue	CT	432+	PR
26	61	Liver, ascites	S, Ox, CT	72	P
27	58	Liver, ascites	S, Ox, CT	200	PR
28	50	Lung	S	91	P
29	69	Lung, pleura	S	315	PR
30	44	Lung	S	42	P

S = surgical therapy; RT = radiation therapy; E = estrogen; A = androgen; C = corticosteroids; PR = progesterone; CT = chemotherapy; Ox = oophorectomy; HPx = hypophysectomy
NC = no change; P = progression; PR = partial response

TABLE 2.—*Summary of Responses to Tamoxifen*

	Number	*Percent*	*Duration in Months*
Partial response	13/28	43	14.1+
No change	7/28	23	6.3+
Progression	8/28	27	..
Withdrawal	2/30	7	..

TABLE 3.—*Summary of Responses According to Dominant Sites*

Sites	*Partial Response*	*No Change*	*Progression*
Soft tissue	2/3	0/3	1/3
Visceral	3/8	1/8	4/8
Osseous	8/17	6/17	3/17

TABLE 4.—*Previous Treatment and Tamoxifen Response*

	Partial Response	*No Change*	*Progression*
Previous Successful Therapy			
Oophorectomy	2/5	1/5	2/5
Hypophysectomy	2/2	0/2	0/2
Estrogen	3/7	3/7	1/7
Androgen	1/3	2/3	0/3
Corticosteroids	0/1	1/1	0/1
Chemotherapy	3/7	2/7	2/7
Previous Unsuccessful Therapy			
Oophorectomy	0/1	0/1	1/1
Estrogen	0/3	0/3	3/3
Androgen	0/4	1/4	3/4
Unevaluable Oophorectomy	0/1	0/1	0/1

less than 25 percent over the original measurement in the product of the two largest perpendicular diameters of measurable lesions with no change in osseous lesions.

- Progression (P). This classification included a 25 percent or greater increase over the original measurement in the product of the two largest perpendicular diameters of measurable lesions or the occurrence of new lesions or the progression of osseous lesions (or combinations of these).

Results

The average age of all patients in the treated group was 63 years, with 10 of the 13 in whom there was response being 61 years old or older. These findings are in agreement with those reported by Morgan and co-workers,[7] who noted patients in whom there was response tended to be older and further past the menopause than patients in whom no response occurred.

Treatment with tamoxifen was carried out in 30 patients. In one patient an intolerable pruritic and papular cutaneous eruption developed which abated after administration of the drug was discontinued and recurred within 24 hours of rechallenge. Administration of the drug was subsequently stopped. In another patient intolerable nausea and vomiting occurred which required discontinuance of tamoxifen therapy. Thus, of the 28 remaining patients, there was a response in 13 (43 percent), no change in disease in 7 (23 percent). All responses were partial (PR) and the mean duration for PR was at least 14.1 months and the mean duration of no change or stable state response was at least 6.3 months. Two patients in whom there was response are still under treatment so that the duration of the mean responses will continue to improve. In eight patients (27 percent) there was no response to administration of the drug and progressive disease developed. These data are tabulated in Table 1 and summarized in Tables 2 and 3.

Previously successful hormonal manipulation, albeit ablative or additive hormonal treatment, usually forecast a favorable response to tamoxifen. Similarly, a previously experienced failure with such hormonal manipulation was predictive of an unlikely response to tamoxifen. These data are noted in Table 4. Although estrogen receptor assays were not done in most patients, it seems reasonable to assume a correlation between the presence of estrogen receptor protein and a beneficial response to tamoxifen therapy. Indeed, *in vitro* tissue culture studies[8,9] and the use of *in vivo*[10] experimental models confirm the competitive binding of tamoxifen with estrogen for receptor sites in hormone dependent tumors.

In most patients, the drug was remarkably free of side effects. In one patient, as previously noted, administration of the drug had to be stopped because a rash developed but in another patient it was possible to continue tamoxifen therapy despite a mild erythema. In two patients nausea occurred; in one of these occasional episodes of vomiting made it necessary to reduce the dosage and then discontinue administration of tamoxifen. In one patient there was an aggravation of a previous thrombocytopenia and although the platelets were reduced to 35,000 per cu mm, no bleeding ensued.

Discussion

The patients in this study represent a selected population: their age was greater than that of

patients in most studies and in two thirds of them response had occurred to previous hormonal manipulation (Table 4).

Although no complete responses were seen, it is apparent from these studies that tamoxifen, a potent antiestrogenic compound, is an effective antitumor agent in women with stage IV cancer of the breast. The median duration of a partial response in this study was 13 months in 43 percent of the treated patients and compares favorably to previously reported results by Cole and associates,[11] Ward,[12] Tormey and co-workers[13] and Manni and associates.[14] Furthermore, in another 23 percent of the patients treated in this study there was no progression of disease for at least another 6.3 months, thereby showing a stable or unchanging disease pattern.

In patients in whom there had been response to hormonal manipulation previously, there usually was response to tamoxifen therapy. In those in whom either hormonal ablation or additive therapy had failed, there rarely was favorable response to tamoxifen administration. These observations agree with those previously published and would likely relate to the presence or absence of an estrogen receptor protein on the tumor cells. Therefore, with the increased availability of estrogen receptor tests, the response to tamoxifen will be more predictable.

The previously reported observation by Pearson and his group that remission or no progression of disease occurred with tamoxifen therapy in five of nine patients in whom hypophysectomies had been done and in one of three patients in whom adrenalectomies had been done was also noted in this study. In one patient in this series, in whom there was response to both oophorectomy and tamoxifen administration, hypophysectomy was later carried out; the patient died from unrelated disease, however, before an evaluable response could be ascertained. Although low levels of estradiol and estrone have been detected in the serum of patients after hypophysectomy, the action of tamoxifen may additionally result from a direct antitumor effect unrelated to its antiestrogenic activity. Another explanation of its favorable action in patients who have undergone hypophysectomy may be related to some positive influence it has upon the immunologic relationship between the tumor and its host.

The adverse side effects of tamoxifen appear to be mild. Because it does not elevate serum desmosterol levels,[15] its use should not be complicated by cataracts which can occur with the use of related compounds such as clomiphene and nafoxidine, other antiestrogenic agents.

It is also noteworthy that exacerbation of disease, such as occurs with estrogen therapy in about a third of patients so treated[16] or with androgen therapy, or even following adrenalectomy,[17] was never definitely observed in any person receiving tamoxifen. This reaction to estrogen ordinarily appears within 14 days of initiating treatment and is characterized by increased pain, progression of cutaneous lesions, hypercalcemia or hypercalciuria or worsening of liver chemistries. Mild transient increases in bone pain occurred in two patients in this study in whom there had been such an exacerbation with pronounced hypercalcemia following estrogen therapy. There seemed to be no side effects with tamoxifen administration. Unfortunately, recent reports[18-20] indicate that hypercalcemia may occur when tamoxifen is used in the treatment of breast cancer.

It was also significant that in three patients in whom chemotherapy had failed with cyclophosphamide, methotrexate and 5-fluorouracil there later was a favorable response (2 PR, 1 NC) to tamoxifen.

It has been shown in this and other studies that tamoxifen is an effective antitumor agent in metastatic breast cancer with minimal side effects. Although it might be considered as an alternate to surgical ablative therapy, the fact that such patients often respond to tamoxifen after ablation implies that both modalities of treatment may be effective in the same person. On the other hand, whether initial therapy with tamoxifen will permit subsequent successful surgical ablation to be effective remains to be evaluated. A few recent reports, as well as the case histories of two patients in this series, suggest that such may be the case. Further data are necessary, however, before the relationship between surgical ablative therapy and antiestrogen treatment is clarified.

Summary

Tamoxifen, an orally administered antiestrogen, was given to 30 patients with stage IV cancer of the breast in a nonrandomized study. Two patients were withdrawn from the study because of adverse drug responses (cutaneous and gastrointestinal, respectively). Of the remaining per-

sons, 13 (43 percent) of the entire group had partial responses with a mean duration of at least 14.1 months. In 23 percent there was stable disease for a mean duration of at least 6.3 months. There were no complete remissions. Two patients are still under therapy with tamoxifen. There was more likely to be a response to tamoxifen therapy in those patients in whom hormonal manipulation had occurred previously, presumably reflecting the presence of estrogen receptor protein.

The drug was essentially free of adverse side effects in most patients. Tamoxifen is a useful agent in the management of advanced cancer of the breast but its role in relation to other hormonal manipulation has yet to be defined.

REFERENCES

1. Harper MJK, Walpole AL: Contrasting endocrine activities of *cis* and *trans* isomers in a series of substituted triphenylethylenes. Nature (London) 212:87, Oct 1, 1966

2. Hahnel R, Twaddle E, Ratajczak T: The influence of synthetic anti-estrogens on the binding of tritiated estradiol-17 by cytosols of human uterus and human breast carcinoma. J Steroid Biochem 4:698-695, 1973

3. Powell-James W, Jenner DA, Blamey RQ, et al: Influence of anti-oestrogens on the specific binding *in vitro* of (3H) oestradiol by cytosol of rat mammary tumor and human breast carcinomata. Biochem J 150:71-75, 1975

4. Cole MP, Jones CTA, Todd IDH: A new anti-oestrogenic agent in late breast cancer—An early clinical appraisal of ICI 46,474. Br J Cancer 25:270-275, 1971

5. Bloom HJG, Boesen E: Anti-oestrogens in treatment of breast cancer: Value of afoxidine in 52 advanced cases. Br Med J 2:7-10, 1974

6. O'Halloran MJ, Maddock PG: ICI 46,474 in breast cancer. J Irish Med Assn 67:38, 1974

7. Morgan Jr LR, Schein PS, Wooley PV et al: Therapeutic use of tamoxifen in advanced breast cancer: Correlation with biochemical parameters. Cancer Treat Rep 60:1437-1443, 1976

8. Lippman M, Bolan G, Huff K: Interactions of antiestrogens with human breast cancer in long-term tissue culture. Cancer Treat Rep 60:1421-1429, 1976

9. Lippman ME, Osborne CK, Knazek R, et al: *In vitro* model systems for the study of hormone-dependent human breast cancer. N Engl J Med 296:154-159, 1977

10. Jordan VC: Anti-estrogenic and anti-tumor properties of tamoxifen in laboratory animals. Cancer Treat Rep 60:1409-1419, 1976

11. Cole MP, Jones CTA, Todd IDH: The treatment of advanced carcinoma of the breast with the anti-oestrogenic agent tamoxifen (ICI 46,474)—A series of 96 patients. Adv Antimicrobi Antineopl Chemother 2:529-531, 1972

12. Ward HWC: Anti-oestrogen therapy for breast cancer: A trial of tamoxifen at two dose levels. Br Med J 1:13-14, 1973

13. Tormey DC, Simon RM, Lippman ME et al: Evaluation of tamoxifen dose in advanced breast cancer. Cancer Treat Rep 60:1451-1459, 1976

14. Manni A, Trujillo J, Marshall JS, et al: Antiestrogen-induced remission in Stage IV breast cancer. Cancer Treat Rep 60:1445-1450, 1976

15. Investigational Drug Brochure for ICI 46, 474. Mar 1974, pp 51-75

16. Nesto RW, Cady B, Oberfield RA, et al: Rebound response after estrogen therapy for metastatic breast cancer. Cancer 38: 1834-1837, 1976

17. Wilson RE, Jessiman AG, Moore FD: Severe exacerbation of cancer of breast after oophorectomy and adrenalectomy: Report of four cases. N Engl J Med 258:312-317, 1958

18. Kiang DT, Kennedy BJ: Tamoxifen (antiestrogen) therapy in advanced breast cancer. Ann Intern Med 87:687-690, 1977

19. Henningsen B, Anberger H: Anti-estrogene Therapie des metastasierenden Mammakarzinoms. Dtsch Med Wochenschr 102: 713-716, 1977

20. Veldhuis JD: Tamoxifen and hypercalcemia. Ann Intern Med 88:574-575, 1978

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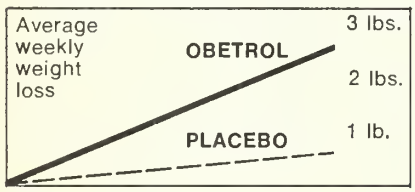

Obetrol eases the discomfort of adherence to a restricted diet in individuals who are well motivated to reduce their food intake.

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Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.
Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.
Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.
Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.
Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.
Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.
Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.
1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
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   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
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Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.
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Examining a Few Myths About Prescribing.

Increasing pressure is being put on the practicing physician to prescribe drugs generically. You are told that brand–name products are universally "expensive" and generic versions are relatively "cheap." To make this case, the most extreme (rather than typical) price differentials are cited. Thus, consumers are led to believe that such differentials are commonplace. Even your knowledge and your motives as a physician are questioned.

Understandably, these views have created myths. We think it's time to examine them in the light of all the facts and ramifications.

MYTH: There are no differences in quality and performance between brand-name products and their generic counterparts. The corollary is that there are no differences among products made by high-technology, quality-conscious, research-based companies and those made by commodity-type suppliers.

FACT: The Food and Drug Administration does a good job in monitoring a generally excellent drug supply. Still, it has nowhere near the resources to guarantee the quality and bioavailability of all marketed products at any given time. Just a few months ago, for example, it noted that batches of tetracycline HCl capsules which met official monograph requirements were not bioequivalent to a reference product. As yo know, there is substanti literature on this subjec affecting many drugs, in cluding such antibiotics as tetracycline and erythromycin. The record o drug recalls and court actions affirms strongly that there are difference among pharmaceutical companies and their products. Research-intensive companies have far better records than those that do no re search and may practic minimum quality assur ance.

MYTH: Industry favors only "expensive" brand names and denigrates all generics.

FACT: PMA companies make 90 to 95 percent o the drug supply, includ ing, therefore, most of t generics. Drug nomenclature is not the impor tant point; it's the comp tence of the manufacturer and the integrity o the product that count.

Matters.

MYTH: Generic options almost always exist.

FACT: About 55 percent of prescription drug expenditure is for single-source drugs. This means, of course, that for only 45 percent of such expenditure, is a generic prescribing option available.

MYTH: Generic prescriptions are filled with inexpensive generics, thus saving consumers large sums of money.

FACT: Market data show that you invariably prescribe—and pharmacists dispense—both brand and generically labeled products from known and trusted sources, in the best interests of patients. In most cases the patient receives a proven brand product. Savings from voluntary or mandated generic prescribing are grossly exaggerated.

MYTH: Drugs account for a major portion of the rise in health care costs.

FACT: Drugs represent a very small part of such costs. The amount of the health care dollar spent for prescription drugs was about 12 cents in 1967; today it is about 8 cents. And you as a physician are most conscious of how drug therapy can cut hospitalization, avert surgery, reduce office visits and keep patients on the job.

MYTH: Government intrusions into the marketplace will save tax money.

FACT: Government schemes always cost the taxpayer something, and the costs often exceed the benefits. Certainly, any federal "help," such as lists of wholesale drug prices sent to all physicians and pharmacists, will be no exception. Just think of the expense of keeping them current! Moreover, wholesale prices are poor guides to actual transaction prices and even worse guides to retail prices.

The PMA Position

We believe your freedom to prescribe, either by generic or brand name, should be totally unabridged. Otherwise, your prescribing prerogatives and your relationships with patients will be seriously impaired.

The maker does matter

After the myths about price and equivalency have been shattered, one fact stands out more clearly than ever: *The maker does matter.* As always, your best guide to drug therapy for your patients is to select products—both brands and generics—from manufacturers with credentials and performance records you have come to respect.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

USING MARIJUANA IN THE REDUCTION OF NAUSEA ASSOCIATED WITH CHEMOTHERAPY—Roger A. Roffman, Division Head for Research Training, Alcoholism and Drug Abuse Institute, University of Washington, Seattle; with forewords by Frederick R. Appelbaum, MD, and Lawrence M. Halpern, PhD, University of Washington. Murray Publishing Company Inc., 2312 Third Avenue, Seattle (98121), 1979. 48 pages, $1.95 plus 50 cents postage & handling charge. (Washington State residents add 11 cents Sales Tax) Quantity prices on request.

ACID-BASE AND POTASSIUM HOMEOSTASIS—Volume 2 in the series: CONTEMPORARY ISSUES IN NEPHROLOGY—Edited by Barry M. Brenner, MD, Samuel A. Levine Professor of Medicine, Harvard Medical School; Director, Laboratory of Kidney and Electrolyte Physiology, and Physician, Peter Bent Brigham Hospital, Boston; and Jay H. Stein, MD, Professor of Medicine and Physiology and Chairman, Department of Medicine, the University of Texas Health Science Center at San Antonio. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 300 pages, $25.00.

ADVANCES IN SHOCK RESEARCH—Volume 1: Editors: Allan M. Lefer, Jefferson Medical College of Thomas Jefferson University, Philadelphia; Thomas M. Saba, Albany Medical College, Albany, NY; and Leena M. Mela, University of Pennsylvania Hospital, Philadelphia—**Volume 2:** Editors: William Schumer, University Health Sciences, Chicago Medical School, Veterans Administration Medical Center, Downey, IL; John J. Spitzer, School of Medicine, Louisiana State University, New Orleans; and Bryan E. Marshall, University of Pennsylvania School of Medicine, Philadelphia. Alan R. Liss, Inc., 150 Fifth Avenue, New York City (10011), 1979. Volume 1, 288 pages, $30.00; Volume 2, 308 pages, $30.00.

BIRTH DEFECTS COMPENDIUM — Second Edition — Editor: Daniel Bergsma, MD, MPH, Clinical Professor of Pediatrics, Tufts University School of Medicine, Boston. Published for the National Foundation—March of Dimes by Alan R. Liss, Inc., 150 Fifth Avenue, New York City (10011), 1979. 1,222 pages, $50.00.

CLEAR SKIN—A Step-by-Step Program to Stop Pimples, Blackheads, Acne—Kenneth L. Flandermeyer, MD, Associate Clinical Professor of Dermatology, University of New Mexico School of Medicine; Illustrated by Monique M. Davis. Little, Brown and Company, 747 Third Avenue, New York City (10017), 1979. 211 pages, $8.95.

CORRELATIVE NEUROANATOMY & FUNCTIONAL NEUROLOGY—Seventeenth Edition—Joseph G. Chusid, MD, Professor of Neurology, New York Medical College; Director, Department of Neurology, St. Vincent's Hospital and Medical Center, New York City. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1979. 464 pages, $12.00.

DATA SUPPLEMENT/COMPUTERIZED TOMOGRAPHY IN CLINICAL MEDICINE—Patricia Davison Laffey, MD, Assistant Professor and Chief, Section of Noninvasive Imaging, Department of Diagnostic Radiology, Wilbur W. Oaks, MD, Professor and Chairman, Department of Medicine, R. Kumar Swami, MD, Senior Instructor, Department of Neurology, J. George Teplick, MD, FACR, Professor and Director of the Division of General Radiologic Diagnosis, Department of Diagnostic Radiology, and Marvin E. Haskin, MD, FACP, FACR, Professor and Chairman, Department of Diagnostic Radiology; all from The Hahnemann Medical College and Hospital of Philadelphia. Medical Directions, Inc., Suite 326, 3 Penn Center Plaza, 15th and Market Streets, Philadelphia (19102), 1978. 52 pages, $16.00.

DRUG INTERACTIONS—Clinical Significance of Drug-Drug Interactions and Drug Effects on Clinical Laboratory Results—Fourth Edition—Philip D. Hansten, Pharm D, Associate Professor of Clinical Pharmacy, College of Pharmacy, Washington State University, Pullman, WA. Lea & Febiger, 600 Washington Square, Philadelphia (19106), 1979. 552 pages, $16.00.

FAMILY HEALTH AND HOME NURSING—The American National Red Cross. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1979. 626 pages, $3.95 (paperback).

FUNDAMENTALS OF ABDOMINAL SONOGRAPHY—A Teaching Approach—Howard W. Raymond, MD, Radiologist and Chief of Ultrasound, Department of Radiology, Union-Truesdale Hospital, Fall River, Massachusetts; Clinical Instructor of Diagnostic Radiology, Brown University Medical School, Providence, RI. Grune & Stratton, Inc., Medical and Scientific Publishers, 111 Fifth Ave., New York City (10003), 1979. 200 pages, $23.00. Distributed in the UK by Academic Press, Inc. (London)Ltd., 24/28 Oval Road, London NW1.

FUNDAMENTALS OF MOBILE CORONARY CARE—Second Edition—Leonard B. Rose, MD, FACP, FACC, Associate Clinical Professor of Medicine, University of Oregon Health Sciences Center, Director, Intensive Care Unit, V.A. Medical Center, Vancouver, WA; and Beatrice K. Rose, MD, MPH, Associate Professor of Preventive Medicine, University of Oregon Health Sciences Center, and Associate Clinical Professor, Division of Health Services, School of Public Health & Community Medicine, University of Washington, Seattle. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1979. 116 pages, $13.00.

HANDBOOK OF MEDICAL TREATMENT—16th Edition—Edited by Milton J. Chatton, MD, Clinical Professor of Medicine, Stanford University School of Medicine. Jones Medical Publications, 355 Los Cerros Drive, Greenbrae, CA (94904), 1979. 643 pages, $10.50.

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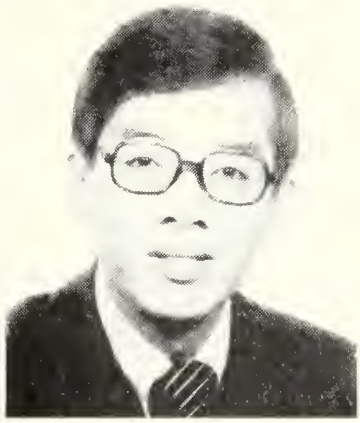

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EMERGENCY DEPARTMENT California, Berkeley-Alameda County: Career-oriented ED physician wanted full-time, with contract group at active hospital. Over 30,000 visits yearly. Salary negotiable. Vacation and educational leave. Contact: C. Ferrell Varner, MD, Herrick Memorial Hospital, 2001 Dwight Way, Berkeley, CA 94704. (415) 845-0130, Ext. 375.

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NEUROLOGY: Board Certified or eligible neurologist sought by multispecialty group. Easy access to community hospitals. Easy driving distance to UCLA and USC Medical Schools. Guaranteed salary or percentage basis. Contact: V. W. Gieschen, MD, 2230 Lynn Rd., Thousand Oaks, Ventura County, CA 91360. Phone (805) 497-7588.

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UCLA FACULTY POSITION—The UCLA Emergency Medicine Center announces the opening of a fulltime academic position. Preference given to graduates of emergency medicine residency programs. Board certified internists and surgeons with career commitments to academic emergency medicine are also invited to apply. Please contact: Charles R. McElroy, MD; or David J. Orban, MD; or Marie K. Silver, MD, Emergency Medicine Center, UCLA Hospital and Clinics, Center for the Health Sciences, 10833 Le Conte, Los Angeles, CA 90024.

SANTA BARBARA, CALIFORNIA: 48 Physician multi-specialty clinic has immediate openings in: Family Practice and Pulmonary Disease. Excellent benefit package. U.S. citizenship, Board certified/eligible. Curriculum Vitae to: Administration, Santa Barbara Medical Foundation Clinic, Box 1200, Santa Barbara, CA 93102.

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(Continued on Page 26)

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(Continued from Page 25)

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PHYSICIAN with 10 years experience in preventive and occupational medicine and postgraduate training for 4 years, seeks position in San Francisco/Bay Area in medical outpatient clinic. Write Box 6020, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ANESTHESIOLOGIST/DIRECTOR large metropolitan outpatient surgery past 5 years. Interested in similar arrangement in scenic smaller community. Will negotiate. Write Box 6062, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PRIMARY CARE INTERNIST, 32, university trained, AOA, ABIM eligible, seeks solo, group, or clinic practice in the West. Available July 1980. Box 6059, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INFECTIOUS DISEASE—INTERNIST ABIM age 31 with impeccable credentials seeks association with group practice in Southern California/West Coast. Write Box 6060, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CRITICAL CARE—INTERNIST—certified, fellowship completed, university trained, available for locum tenens—will consider hospital or private practice opportunities. Prefer San Francisco Bay area. Write Box 6058, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

EMERGENCY NURSE PRACTITIONER available for primary or back-up coverage for your Emergency Department. Available January 1980. Contact: R. Wright, 3833 No. 30th St., No. 122, Phoenix, AZ 85016.

INTERNIST—32, board certified, Harvard-Stanford trained; seeks position in East Bay/West Contra Costa County. Write Box 6063, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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DERMATOLOGIST, also board certified in Peds, available for locum tenens in Northern California or northwest states from November 1979 to June 1980. Replies: A. L. Cowan, MD, 347 Amalti Dr., Santa Monica, CA 90402.

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INFORMATION

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EX 220

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FAMILY PRACTICE—West Los Angeles. Well established solo practice by Board Certified physician. High gross/net with excellent growth potential. Includes x-ray, lab, EKG, microtherm. Dr. willing to introduce patients. Attractive medical assistant/xray technician employed 14 years available. Phone (213) 826-8810.

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ANESTHESIOLOGY

September 15-22—**Practical Management of Anesthetic Problems.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 31½ hrs. $325.

September 29-30—**Pharmacology and Anesthesia.** California Society of Anesthesiologists at Doubletree Inn, Monterey. Saturday-Sunday. 9 hrs. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

October 20-24—**American Society of Anesthesiologists—Annual Meeting.** Hilton, San Francisco. Saturday-Wednesday. Contact: William S. Marinko, Asst. Exec. Sec., ASA, 515 Busse Highway, Park Ridge, IL 60068. (312) 825-5586.

October 25-November 2—**Post ASA Hawaiian Seminar.** Kona Village Resort, Hawaii. 9 days. 28 hrs. Contact: Adham Safwat, Box 7550, Menlo Park 94025. (415) 494-3799.

October 26-28—**Clinical Anesthesia Monitoring.** Anesthesiology Educational Foundation and Calif. Soc. of Anesthesiologists at Holiday Inn, Monterey. Friday-Sunday. Contact: AEF, P.O. Box 24230, Federal Bldg., Los Angeles 90024.

January 8-12—**Anesthesia Update.** UCSD at Hotel del Coronado. Tuesday-Saturday. 20 hrs. $200.

January 25-27—**Pediatric Anesthesiology—18th Clinical Conference.** Childrens Hospital at Marriott, Los Angeles. Thursday-Saturday. 15 hrs. $160. Contact: Wayne Herbert, MD, P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

February 7-10—**7th Neonatal and Infant Respiratory Symposium.** Ohio State Univ., Dept. of Anesthesiology, at Marriott, Los Angeles. Thursday-Sunday. Contact: John S. McDonald, MD, Dept. of Anesthesiology, OSU, 410 W. 10th Ave., Columbus, OH 43210. (614) 422-5591.

CANCER

September 15—**Histopathology of Head and Neck Tumors.** Head and Neck Cancer Network of the No. Calif. Cancer Program and San Francisco Regional Cancer Foundation at Children's Hospital, San Francisco. Saturday. 8 hrs. Contact: SF Regional Cancer Fnd., 14th and Lake, San Francisco 94118. (415) 221-2132.

September 15-16—**Advances in the Cause, Detection and Prevention of Cancer: A Multi-Disciplinary Analysis.** UCSF at Sheraton-Palace, San Francisco. Saturday-Sunday.

September 20-22—**Bladder Cancer.** American Urological Assn. at Hilton Hotel, San Diego. Thursday-Saturday. 16 hrs. $200, memoers; $250, nonmembers. Contact: Mary Rohan, AUA Office of Education, P.O. Box 1129, Aspen, CO 81611. (303) 925-2012.

September 26—**Head and Neck Cancer Symposium.** Hospital of the Good Samaritan, Los Angeles. Wednesday. 7 hrs. Contact: Janie Sternal, CME Coordinator, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

October 12—**John W. Cline Memorial Lecture.** American Cancer Society, Calif. Division, at Woodlake Inn, Sacramento. Friday. Contact: Education Dept., ACS, 731 Market, San Francisco 94103. (415) 777-1800.

October 13-20—**New Approaches to the Evaluation of Neoplastic Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 33½ hrs. $375.

October 27—**New Methods for Fighting Cancer.** San Francisco Regional Cancer Foundation at Letterman Army Hospital, San Francisco. Saturday. 4 hrs. Contact: Dr. Terry Sheehy, S.F. Regional Cancer Foundation, 14th and Lake, San Francisco 94118. (415) 221-2132.

October 31-November 2—**Cancer Symposium—3rd Annual.** Scripps Memorial Hospital at Holiday Inn at the Embarcadero, San Diego. Wednesday-Friday. 22 hrs. $250. Contact: Nomi Feldman, Conf. Coordinator, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

November 9-10—**Gynecologic and Breast Cancer: Current Concepts and Controversies.** Mt. Zion Hospital and Medical Center at Fairmont Hotel, San Francisco. Friday-Saturday. Contact: Office of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

December 12—**15th Annual Northern California Cancer Conference.** N. T. Enloe Memorial Hospital at Holiday Inn,

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Lolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

Chico. Wednesday. 7 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Memorial Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 284.

January 16—**Testicular Tumors.** Hospital of the Good Samaritan at Bonaventure, Los Angeles. Wednesday. Contact: Janie Sternal, Cont. Med. Ed., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

EMERGENCY MEDICINE

September 17-21—**Topics in Emergency Medicine.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Monday-Friday. 40 hrs. $325.

September 24—**Trauma—Auto and Motorcycle Patients.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

September 24-28—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Monday-Friday. 40 hrs. $350.

October 8-12—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

November 30-December 1—**Emergency Medicine.** UCLA. Friday-Saturday.

December 6-7—**Advances in Emergency Medicine.** UCSF. Thursday-Friday.

December 6-8—**Trauma.** See Surgery, December 6-8.

December 10-14—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $350.

January 14-18—**Medical Management of EMS Systems.** UCSD at Hilton, San Diego, Monday-Friday. 36 hrs.

January 21-25—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

January 21-25—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

February 11-15—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

MEDICINE

September 16-20—**Pacific Dermatologic Association—Annual Meeting.** Hyatt Regency, San Francisco. Sunday-Thursday. 15½ hrs. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno NV 89509. (702) 323-2461.

September 24-28—**An Advanced Course for Internists.** STAN at San Francisco. Monday-Friday.

September 28-30—**Coronary Disease, Exercise Testing and Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton on the Wharf, San Francisco. Friday-Sunday. 13 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

October 3-4—**47th Annual Fall Symposium and 12th George C. Griffith Scientific Lecture.** American Heart Assn., Greater Los Angeles Affiliate, at Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hrs. $85, member any Heart Assn.; $110, nonmember. Contact: Alexis Krieger, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

October 3-December 12—**Hematology/Oncology for the Practicing Internist.** UCLA. Wednesday evenings.

October 5-6—**Controversial Issues in Internal Medicine—24th Annual Symposium.** Southern California Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, Ed. and Research Dept., SCPMG, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

October 6—**Office Allergy.** PMC. Saturday. 6 hrs. $85.

October 8—**Calcium Metabolism.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

October 9—**10th Annual Paul M. Aggeler Lecture—Paroxysmal Nocturnal Hemoglobinuria—Present Status and Future Prospects.** San Francisco General Hospital and UCSF at San Francisco General Hospital. Tuesday. Contact: Susan Nutter, SF Gen. Hosp., 1001 Potrero, Rm. 4101, San Francisco 94110. (415) 821-8571.

October 10—**Autoimmune Hemolytic Anemia and Destruction of Red Cells.** San Francisco General Hospital and UCSF at UCSF. Wednesday. Contact: Susan Nutter, SF Gen. Hosp., 1001 Potrero, Rm. 4101, San Francisco 94110. (415) 821-8571.

October 10—**Rheumatoid Arthritis—Its Diagnosis and Treatment.** LLU. Wednesday. 4 hrs.

October 11-12—**49th Annual Physicians' Postgraduate Symposium on Cardiovascular Disease.** American Heart Assn., San Francisco Chapter, at San Franciscan Hotel, San Francisco. Thursday-Friday. Contact: Patty MacJennett, AHA, 421 Powell St., San Francisco 94108. (415) 433-2273, ext. 443.

October 13—**Lupus Erythematosus.** UCSD. Saturday. 6 hrs. $45.

October 14—**Coronary and Valvular Heart Disease—Update 1980—2nd Annual Health Symposium.** Northridge Hospital Medical Center and Southern Calif. Heart Center at Century Plaza, Los Angeles. Sunday. Contact: Northridge Hosp. Med. Ctr., 18300 Roscoe Blvd., Northridge 91324. (213) 885-5339.

October 15-19—**Advanced Course for Internists.** STAN at Hyatt on Union Square, San Francisco. Monday-Friday. 25 hrs. $290.

October 18-20—**Cardiology Update—1979.** American College of Cardiology at Del Monte Hyatt, Monterey. Saturday-Monday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

October 18-20—**Rheumatology Update—1979.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Saturday. 16 hrs. $165.

October 18-21—**Society of Nuclear Medicine—4th Annual Western Regional Meeting.** Monterey Conference Center, Monterey. Thursday-Sunday. Contact: Justine Parker, Western Regional Chapters, Society of Nuclear Medicine, P.O. Box 40279, San Francisco 94140. (415) 647-0722.

October 19-20—**Mycology Review** (a course for residents in dermatology and pathology). STAN. Friday-Saturday. 16 hrs. $50 per day; $25 per day for residents and trainees. Contact: Paul H. Jacobs, MD, Dept. of Derm., Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

October 19-20—**Vascular Disorders and the Primary Care Physician.** UCSF at Fairmont Hotel, San Francisco. Friday-Saturday. 11 hrs. $130, both days; $80, one day.

October 20-27—**British Clinical Cardiology in the Paul Wood Tradition.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $325.

October 22—**Respiratory Diseases Due to Pollutants.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

October 24—**Diabetes Mellitus Symposium.** Hospital of the Good Samaritan at Biltmore, Los Angeles. Wednesday. 7 hrs. $70. Contact: Janie Sternal, Cont. Med. Ed., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

November 1-2—**Symposium on Thyroid Disease, Parathyroid Disease, and Vitamin D Metabolism.** Providence Hospital and Endocrine-Metabolic Center at Hilton, San Francisco. Thursday-Friday. 18 hrs. $200. Contact: Endocrine-Metabolic Ctr., P.O. Box 23020, Oakland 94623. (415) 835-4940.

November 2-3—**California Society of Internal Medicine—Annual Meeting.** Hotel del Coronado, Coronado. Friday-Saturday. Contact: CSIM, 703 Market St., 1412 Central Tower, San Francisco 94103. (415) 362-1548.

November 3—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Sch. of Med., Stanford 94305. (415) 497-6101.

November 4-6—**Fifth Annual Workshop on the Thyroid.** American Thyroid Assn. at Golden Gateway Holiday Inn,

San Francisco. Sunday-Tuesday. 14 hrs. $200. Contact: Dr. Lewis Braverman, Univ. of Mass. Med. Ctr., 55 Lake Ave., N., Worchester, MA 01605.

November 5-9—**Update on Dermatology and Rheumatology for the Practicing Physician.** Scripps Clinic and Research Foundation at Islandia Hyatt, San Diego. Monday-Friday. 35 hrs. $325. Contact: Nomi Feldman, Conf. Coordinator, Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100, ext. 8214.

November 5-14—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

November 8-10—**Coronary Artery Disease: Medical and Surgical Decisions.** Eisenhower Medical Center at Marriott Las Palmas Resort, Rancho Mirage. Thursday-Saturday. Contact: John J. Deller, MD, Dir. of Ed. and Research, Eisenhower Med. Ctr., 39000 Bob Hope Dr., Palm Desert 92260. (714) 346-3911.

November 9—**Venous Thromboembolism.** PMC and American Heart Assn. Friday. 6 hrs. $25.

November 10—**Viral Diseases in Clinical Practices.** Alta Bates Hospital, Berkeley. Saturday. 6 hrs. Contact: Claudia Read, Med. Ed., Alta Bates Hosp., 3001 Colby St., Berkeley 94705. (415) 845-7110, ext. 2055.

November 10-11—**Practical Nephrology for the Primary Care Physician.** UCLA. Saturday-Sunday.

November 15-16—**Neurology Update.** UCSD at Vacation Village, San Diego. Thursday-Friday.

November 15-17—**Advanced Cardiopulmonary Care.** PMC at Holiday Inn-Financial District/Presbyterian Hospital, San Francisco. Thursday-Saturday. 12 hrs. lecture; 18 hrs. lecture and workshop. $150 for lecture; $235, lecture and workshop.

November 30-December 2—**Concepts of Common Infectious Diseases.** UCSD at Hilton, San Diego. Friday-Sunday. 15 hrs. $175.

December 1-2—**Practical Endocrinology for Primary Care Physicians.** UCLA. Saturday-Sunday.

December 6-7—**5th Annual Lyman A. Brewer, III, Cardiothoracic Symposium—The Esophagus.** White Memorial Medical Center at Bonaventure Hotel, Los Angeles. Thursday-Friday. Contact: Dir., Dept. of CME, White Memorial Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 263-6100 or (213) 268-5000.

December 6-9—**Neurotology Workshop.** PMC at Ilikai Hotel, Honolulu. Thursday-Sunday. 24 hrs. $435.

December 7-8—**Allergy/Immunology, Infectious Diseases, Endocrinology/Metabolism, Oncology.** American College of Physicians at San Francisco. Friday-Saturday. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200.

December 7-9—**Advances in Heart Disease 1980—12th Annual Seminar on Clinical Cardiology.** American College of Cardiology at Fairmont Hotel, San Francisco. Friday-Sunday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

December 12—**Management of Hypertension.** LLU. Wednesday. 4 hrs.

January 2—**Practical Gastroenterology for Primary Care Physicians.** UCLA. Saturday.

January 6-13—**Echocardiography in Hawaii.** Honolulu Medical Group Research and Education Foundation, Univ. of Hawaii School of Medicine, Univ. of Rochester School of Medicine at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 18 hrs. Contact: Echocardiography in Hawaii, Honolulu Med. Grp. Research and Ed. Fnd., 550 S. Beretania St., Honolulu 96813. (808) 537-2211.

January 8-12—**Intensive Review of Common Allergic and Asthmatic Diseases.** UCD at Inter-Continental Hotel, Maui, Hawaii. Tuesday-Saturday. 25 hrs. $250.

January 20-24—**Angiography and Vascular Disease.** UCSD at Vacation Village, San Diego. Sunday-Thursday. 26 hrs. $325.

January 26—**Asthma and Allergies.** UCLA. Saturday.

January 31-February 2—**Fundamentals of Echocardiography—An Introductory Course for Clinicians.** American College of Cardiology at Century Plaza, Los Angeles. Thursday-Saturday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 2—**Pediatric Dermatology Seminar.** STAN. Saturday. Contact: Paul H. Jacobs, MD, Dept. of Derm., Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

February 7-9—**Tri-State Symposium on Clinical Cardiology.** American Heart Assn.'s Council on Clinical Cardiology; AHA, Greater Los Angeles, Arizona and New Mexico Affiliates, at Disneyland Hotel, Anaheim. Thursday-Saturday. 15 hrs. $200, Heart Assn. member; $250, nonmember. Contact: LaVerna Titus, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

February 13—**Chronic Obstructive Pulmonary Disease.** LLU. Wednesday. 4 hrs.

February 13-15—**Advances in Neurology.** UCSF. Wednesday-Friday.

February 13-15—**Cardiovascular Disease—1980: Advances in Diagnosis and Management.** American College of Cardiology at Vacation Village, San Diego. Wednesday-Friday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 16—**5th Annual Liver Conference, Cholestasis.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 7 hrs. $105. Contact: Prog. Coord., Ctr. for Health Ed., 2801 Atlantic Ave, Long Beach 90801. (213) 595-3811.

February 22-23—**Medical Knowledge Self Assessment II.** American College of Physicians and PMC at Hyatt Regency, San Francisco. Friday-Saturday. 12 hrs. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

OBSTETRICS AND GYNECOLOGY

October 4-6—**Update in Obstetrics.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Saturday. 14 hrs. $175.

October 17-21—**Pacific Coast Fertility Society—27th Annual Meeting.** Marriott's Rancho Las Palmas, Rancho Mirage. Wednesday-Sunday. Contact: PCFS, 5820 Wilshire Blvd., Suite 500, Los Angeles 90036. (213) 937-5514.

November 5-8—**Advancing Perinatology into the 1980's.** UCSD at Vacation Village, San Diego. Monday-Thursday.

November 9-11—**Peripartum Period.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Friday-Sunday. 6 hrs. $150. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 29-December 1—**High-Risk Pregnancy—3rd Annual Conference.** Memorial Hospital Medical Center-UCI Center for Health Education at Canyon Hotel, Palm Springs. Thursday-Saturday. 18 hrs. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 6-8—**Gynecologic Urology: Theory and Practice, Basic and Advanced.** Memorial Hospital Medical Center-UCI Center for Health Education at Sheraton-Universal, Hollywood. Thursday-Saturday. 20 hrs. $300. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 7-8—**Adolescent Sexuality and Gynecology.** PMC Friday-Saturday. 9 hrs. $125.

February 9-10—**Obstetrical and Gynecological Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton, Beverly Hills. Saturday-Sunday. 10 hrs. $70. Contact: Miss Dee Davis, Exec. Sec., 5820 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

PEDIATRICS

September 19-20—**36th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Hilton Hotel, Los Angeles. Wednesday-Thursday. Contact: LAPS, P.O. Box 2022, Inglewood 90305.

September 28-29—**Practical Pediatrics With Doctor Sydney Gellis.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 9 hrs. $80.

October 12—**Symposium on Sudden Infant Death Syndrome.** National SIDS Foundation, N. Calif. Chap., and Children's Hosp. Medical Center at Goodman Hall, Jack London Square, Oakland. Friday. 7 hrs. $50. Contact: Patricia Bail, 825 Paru St., Alameda 94501. (415) 865-2714.

October 13—**The Hearing Impaired Child.** Peninsula Hosp. and San Mateo Co. Office of Education at Peninsula Hosp., Burlingame. Saturday. Contact: Susan M. Norrell, Neurosensory Ctr., Peninsula Hosp., 1783 El Camino, Burlingame 94010. (415) 697-4061, ext. 479.

October 13-18—**American Academy of Pediatrics—Annual Meeting.** Hilton Hotel and Brooks Hall, San Francisco. One week. 33-36 hrs. $60, members; $120, nonmembers. Contact: W. G. Janzen, Meeting Mgr., AAP, 1801 Hinman Ave., Evanston, IL 60204. (312) 869-4255.

November 12-14—**Primary Care Pediatrics.** UCI at Marriott Inn, Newport Beach. Monday-Wednesday. 17 hrs.

November 16-19—**Las Vegas Seminars.** American Academy of Pediatrics, Calif. Chapters 1, 2, 3, at Hilton Hotel, Las Vegas. Friday-Monday. $175, members; $200, nonmembers. Contact: AAP, Chap. 2, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

November 26-29—**Developmentally Disabled Child.** UCSD at Vacation Village, San Diego. Monday-Thursday.

December 6-8—**Pediatric Allergy/Immunology.** UCSF. Thursday-Saturday.

February 2—**Pediatric Dermatology Seminar.** See Medicine, February 2.

PACIFIC MEDICAL CENTER

Course Offerings August-December, 1979

AUGUST 18
Strabismus

SEPTEMBER 10-13
EKG Self Assessment

SEPTEMBER 20
Transfusion Therapy in Clinical Practice

*OCTOBER 5
Interviewing Skills in Psychiatry I

OCTOBER 6
Allergy in Office Practice

NOVEMBER 9
Treatment of Venous and Thromboembolic Disease

NOVEMBER 15-17
Advanced Cardiopulmonary Care

DECEMBER 6-9
Neurotology Workshop

DECEMBER 7-8
Medical Knowledge Self Assessment Test I

DECEMBER 7-8
Adolescent Sexuality & Gynecology

*This course will be repeated at varying locations on October 26, November 3, November 16, and December 14

For further information write:
Continuing Education
P.O. Box 7999, San Francisco, CA 94120
Tel. (415) 563-4321 Ext 2761

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February 4-6—**Pediatric Nephrology and Urology.** UCSD at Vacation Village, San Diego. Monday-Wednesday.

PSYCHIATRY

September 15—**Psychopharmacology in Clinical Practice: A Practicum in Mind-Allergy Drugs.** UCLA. Saturday.

September 15—**The Significance of Psychotherapy in the Treatment of Schizophrenic Illness.** No. Calif. Psychiatric Society and McAuley Institute at St. Mary's Hospital, San Francisco. Saturday. 3 hrs. $15. Contact: NCPS, 1631 Ocean Ave., San Francisco 94112.

October 1-November 29—**Special Problems in Psychotherapy.** So. Calif. Psychoanalytic Institute at various southern Calif. locations. 5 sessions on various evenings. 10 hrs.; 2 hr. per session. $50. Contact: Mrs. Alva Lane, SCPI, 9024 Olympic Blvd., Beverly Hills 90211. (213) 276-2455.

October 3-31—**Object Relations.** Southern Calif. Psychoanalytic Institute, Beverly Hills. 5 Wednesdays; 8:00-10:00 p.m. Contact: Mrs. Alva Lane, SCPI, 9024 Olympic Blvd., Beverly Hills 90211. (213) 276-2455.

October 3-31—**Techniques for Superego Modification: Fighting the Cruel Conscience.** Southern Calif. Psychoanalytic Institute, Beverly Hills. 5 Wednesdays; 7:30-9:30 p.m. Contact: Mrs. Alva Lane, SCPI, 9024 Olympic Blvd., Beverly Hills 90211. (213) 276-2455.

October 3-November 28—**Split Brains, Alexithymia and Psychoanalysis.** Southern Calif. Psychoanalytic Institute, Beverly Hills. 5 Wednesdays; 8:00-10:00 p.m. Contact: Mrs. Alva Lane, SCPI, 9024 Olympic Blvd., Beverly Hills 90211. (213) 276-2455.

October 5—**Interviewing Skills in Psychiatry.** PMC at Sacramento. Friday. 4 hrs. $25.

October 12-14—**Infant Psychiatry II.** UCSF. Friday-Sunday.

October 13—**Explorations of Healing in Psychotherapy.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 6 hrs. $60.

October 20—**The Borderline Personality—Diagnosis and Treatment.** Northern Calif. Psychiatric Society and McAuley Institute at St. Mary's Hospital, San Francisco. Saturday. 3 hrs. $15. Contact: NCPS, 1631 Ocean Ave., San Francisco 94112.

October 26—**Interviewing Skills in Psychiatry.** PMC at Los Angeles. Friday. 4 hrs. $25.

October 27—**Psychiatry Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 7 hrs. Contact: Prog. Coordinator, UCI Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 28-31—**Academy of Psychosomatic Medicine—Annual Meeting.** Fairmont Hotel, San Francisco. Sunday-Wednesday. Contact: Thomas C. Nelson, Exec. Dir., 70 W. Hubbard, Suite 202, Chicago, IL 60610. (312) 644-2623.

October 28-31—**Therapeutic Guided Imagery.** UCLA at Yosemite. Sunday-Wednesday.

November 3—**Current Concepts in Sleep Disorders.** Northern Calif. Psychiatric Society and McAuley Institute at St. Mary's Hospital, San Francisco. Saturday. 3 hrs. $15. Contact: NCPS, 1631 Ocean Ave., San Francisco 94112.

November 3—**Interviewing Skills in Psychiatry.** PMC. Saturday. 4 hrs. $25.

November 9-11—**World of Family Therapy Symposium.** UCSF. Friday-Sunday. 10 hrs. $55.

November 16—**Interviewing Skills in Psychiatry.** PMC at San Diego. Friday. 4 hrs. $25.

November 26-30—**Group Therapy Seminars.** UCSF at VA Hospital, Oakland. Monday-Friday. 31 hrs. $50.

December 14—**Interviewing Skills in Psychiatry.** PMC at Anaheim. Friday. 4 hrs. $25.

January 18-20—**Brief Psychotherapy.** UCSF. Friday-Sunday.

February 2—**Dealing with Depression.** UCLA. Saturday.

February 9-10—**Sexual Therapy.** UCLA. Saturday-Sunday.

RADIOLOGY AND PATHOLOGY

September 15—**Emergency Radiology—7th Annual Radiology Symposium.** Southern California Permanente Medical Group at Century Plaza Hotel, Los Angeles. Saturday. Contact: Catherine Andrews, Ed. and Research Dept., SCPMG, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4516.

October 6—**Radiology and Trauma.** UCI at Grand Hotel, Anaheim. Saturday. 6 hrs.

October 13-21—**International Body Imaging Conference—4th Annual.** West Park Hospital, Canoga Park, at Royal Lahaina Hotel, Maui, Hawaii. 9 days. 30 hrs. $295. Contact: Conf. Sec., Imaging Conf., West Park Hosp., Dept. of Radiology, 22141 Roscoe Blvd., Canoga Park 91304.

October 18-20—**New Advances and Controversies in Neuroradiology.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. 17 hrs. $190.

October 18-21—**Society of Nuclear Medicine—4th Annual Western Regional Meeting.** See Medicine, October 18-21.

October 19-20—**Mycology Review** (a course for residents in dermatology and pathology). See Medicine, October 19-20.

November 2-4—**Radiology of the Gastrointestinal System (II).** American College of Radiology at San Francisco. Friday-Sunday. 15 hrs. $275. Contact: Maurice H. Trautz, Dir. of Ed., ACR, 6900 Wisconsin Ave., Chevy Chase, MD 20015. (301) 654-6900.

November 5—**American Association of Blood Banks—Annual Meeting.** Hilton Convention Center, Las Vegas. Monday. Contact: AABB, Suite 608, 1028 L St., NW, Washington, DC 20001.

November 12-14—**Liquid Chromatography in Clinical Analysis.** UCSF at Golden Gateway Holiday Inn, San Francisco. Monday-Wednesday. 19 hrs. $200.

January 9—**Gastrointestinal Radiology and Diagnosis.** LLU. Wednesday. 4 hrs.

January 26-27—**Modern Gastrointestinal Radiologic Techniques for Practicing Physicians.** UCSF at Fairmont, San Francisco. Saturday-Sunday. 13 hrs. $200.

January 28-February 1—**Computed Tomography.** UCSF. Monday-Friday.

January 30-February 1—**Genito-Urinary Pathology—7th Annual Course.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 22½ hrs. $220. Contact: Prog. Coord., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 1-3—**Neuroradiology.** UCSF at Fairmont, San Francisco. Friday-Sunday. 20 hrs. $190.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 23 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

September 24—**Trauma—Auto and Motorcycle Patients.** See Emergency Medicine, September 24.

October 4-6—**Advances and Controversies in Vascular Surgery.** Cedars-Sinai Medical Center at Century Plaza Hotel, Los Angeles. Thursday-Saturday. 19 hrs. $195. Contact: Lore Kahane, Room 2049, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles 90048. (213) 855-5547.

October 6—**Update of Pediatric Opthalmology.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $85. Contact: Lu Hendricks, Jules Stein Eye Inst., UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

October 11-13—**Surface Replacement of the Hip.** UCLA. Thursday- Saturday.

October 19-20—**Cataract Surgery Pragmatics.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 16 hrs. $175. Contact: Program Coordinator. Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 585-3811.

October 28-November 9—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200, otolaryngologists; $900, residents. Contact: Antonio De La Cruz, MD, Ear Research Inst., 256 S. Lake St., Los Angeles 90057.

November 5-9—**American Academy of Ophthalmology.** Civic Auditorium, San Francisco. Monday-Friday. Contact: Faye Anderson, Dir. of Mtgs., P.O. Box 7424, San Francisco 94120. (415) 563-5725.

November 24-December 1—**International Seminar on Operative Arthroscopy.** UCLA at Kauai, Hawaii. One week. 39 hrs. $650, with laboratories; $450 without laboratories.

December 6-8—**Trauma.** No. Calif. Chap. Committee on Trauma of the American College of Surgeons at Claremont Resort Hotel, Oakland. Thursday-Saturday. Contact: F. William Blaisdell, MD, Dept. of Surg., UCD Sch. of Med., Rm. 257, 4301 X St., Sacramento 95817. (916) 453-2207.

December 6-8—**Gynecologic Urology.** See Obstetrics and Gynecology, December 6-8.

December 8—**Blepharoplasty and Other Cosmetic Surgery of the Eyelid.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

December 6-9—**Neurotology Workshop.** See Medicine, December 6-9.

January 14-18—**Otologic Surgery Course—15th Annual.** Ear Research Institute, Los Angeles. Monday-Friday. 40 hrs. $500. Contact F. H. Linthicum, Jr., MD, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

January 22-June 14—**Recent Advances in Surgical Science.** UCLA at Wadsworth VA Hospital, Los Angeles. One evening/month.

January 31-February 2—**Calculi.** American Urological Assn. at San Francisco. Wednesday-Friday. Contact: Office of Education, AUA, P.O. Box 1129, Aspen, CO 81611. (303) 925-2018.

February 6-8—**Annual Ophthalmology Course.** UCSF. Wednesday-Friday.

February 6-8—**Plastic Surgery.** UCLA. Wednesday-Friday.

February 7-9—**Vascular Surgery.** UCSF. Thursday-Saturday.

February 8-9—**Cataract Surgery and Intraocular Lenses: Planned Extracapsular, Phacoemulsification and Intracapsular Techniques.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $450. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

February 14-15—**Head and Neck Trauma.** UCSF. Thursday-Friday.

OF INTEREST TO ALL PHYSICIANS

September 15—**Psychopharmacology in Clinical Practice: A Practicum in Mind-Allergy Drugs.** See Psychiatry, September 15.

September 20—**California Venereal Disease Controllers' Clinical Session.** CMA Task Force on Venereal Disease, Calif. VD Controllers Assn. and Calif. Academy of Preventive Medicine at San Mateo. Thursday. Contact: Karin McGhee, CMA.

September 20—**Transfusion Therapy in Clinical Practice.** PMC and Irwin Memorial Blood Bank. Thursday. 6 hrs. $85.

September 23-28—**Stress: Harnessing Its Energy for Health.** UCD at Esalen Institute, Big Sur. Sunday-Friday. 30 hrs. $550.

September 28-30—**Physicians—Stress and Coping.** CMA and UCD at Palo Mesa, Fallbrook. Friday-Sunday. 7 hrs. $75/person; $125/couple. Contact: Gail Jara, CMA.

October 1-3—**Integrating Behavioral Science in Family Medicine Setting.** UCI at Balboa Bay Club, Newport Beach. Monday-Wednesday. 17 hrs.

October 5-7—**Physicians—Stress and Coping.** CMA and UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Friday-Sunday. 7 hrs. $75/person; $125/couple. Contact: Gail Jara, CMA.

October 8-12—**American Medical Association—Regional Meeting.** Ilikai Hotel, Honolulu. Monday-Friday. Contact: J. Kelso, AMA, 535 N. Dearborn St., Chicago 60610.

October 8-12—**Hawaii Medical Association.** Ilikai Hotel, Honolulu. Monday-Friday. Contact: J. Won, Exec. Dir., HMA, 320 Ward Ave., Suite 200, Honolulu 96814.

October 11-13—**Western Occupational Medical Association.** Monterey. Thursday-Saturday. Contact: B. H. Bravinder, P.O. Box 201, Alamo 94507.

October 13-21—**International Body Imaging Conference—4th Annual.** West Park Hospital at Royal Lahaina Hotel, Maui, Hawaii. 9 days. 30 hrs. $295. Contact: Conference Sec., Imaging Conf., West Park Hospital, Dept. of Radiology, 22141 Roscoe Blvd., Canoga Park 91304.

October 14-15—**Advances in Alcoholism Symposium.** UCSD and Raleigh Hills Foundation at Newporter Inn, Newport Beach. Sunday-Monday. 14 hrs. $150. Contact: Robert E. Schmitz, MD, Raleigh Hills Fnd., 881 Dover Dr., No. 20, Newport Beach 92663. (714) 645-4310.

October 15-18—**Family Practice Update—4th Annual.** LLU. Monday-Thursday. 27 hrs. $200.

October 28-31—**California Academy of Family Physicians—Annual Scientific Assembly.** Masonic Auditorium, San Francisco. Sunday-Wednesday. Contact: CAFP, 9 First St., San Francisco 94105. (415) 982-6091.

November 1-3—**Postgraduate Institute on Human Sexuality.** CMA, UCD, UCLA, UCSF, UCSD, UCI at Erawan Gardens, Indian Wells. Contact: Charlotte Newhart, CMA.

November 2-4—**Physicians—Stress and Coping.** CMA and UCD at Pajaro Dunes, Watsonville. Friday-Sunday. 7 hrs. $75/person; $125/couple. Contact: Gail Jara, CMA.

November 3—**Exercise: Health Hazards and Benefits.** UCLA. Saturday. 5½ hrs. $85.

November 4-7—**Southern Medical Association.** MGM Grand Hotel, Las Vegas. Sunday-Wednesday. In addition to 21 SMA programs, 22 postgraduate courses presented by AMA's Council on Cont. Physician Ed. Contact: SMA, 2601 Highland Ave., Birmingham, AL 35205.

November 5-9—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $290.

November 12-17—**American Society of Clinical Hypnosis—22nd Annual Scientific Meeting and Workshops.** San Francisco. Monday-Saturday. 40 hrs. $75, scientific program; $250, workshops. Contact: William F. Hoffman, Jr., Exec. Dir., 2400 E. Devon Ave., Suite 218, Des Plaines, IL 60018.

November 14—**Antibiotics.** LLU. Wednesday. 4 hrs.

November 26-30—**Postgraduate Institute for Primary Care Physicians.** UCSD at Hilton Hotel, San Diego. Monday-Friday. 40 hrs.

November 30—**The Many Faces of Shock—1979.** Daniel Freeman Hospital at Hyatt House, Los Angeles. Friday. 6 hrs. $90. Contact: Donald A. Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Hosp., 333 N. Prairie Ave., Inglewood 90301. (213) 674-7050.

November 30-December 2—**Physicians—Stress and Coping.** CMA and UCD at Greenwood Lodge, Soquel. Friday-Sunday. 7 hrs. $75/person; $125/couple. Contact: Gail Jara, CMA.

December 5-7—**Prevention in Primary Care.** UCSD at Vacation Village, San Diego. 20 hrs. $200.

December 9-11—**Nutritional Care of the Hospitalized Patient.** UCSF. Sunday-Tuesday.

January 8-March 25—**Clinical Acupuncture and Stimulation Produced Analgesia.** UCLA. Tuesday evenings.

January 12—**How to Get a Good Night's Sleep.** UCLA. Saturday.

January 12-13—**Current Drug Therapy in the Office.** UCLA. Saturday-Sunday.

January 21-25—**Therapy: Principles and Use of Drugs.** STAN at Hyatt on Union Square, San Francisco. Monday-Friday. 25 hrs. $290.

January 30-February 2—**Primary Care: Current Management of Common Office Problems.** UCSF. Wednesday-Friday.

February 1-7—**LLU Alumni Association—48th Annual Postgraduate Convention.** One week.

February 4-9—**Family Practice Refresher Course—11th Annual.** UCI at Marriott Inn, Newport Beach. Monday-Saturday.

February 7-13—**California Medical Association—109th Annual Session.** Town and Country, San Diego. Thursday-Wednesday. Contact: Rocki Lai, CMA.

February 9-10—**Sexual Therapy.** See Psychiatry, February 9-10.

February 14-15—**Management of the Ventilator Dependent Patient.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. 14 hrs. Contact: Prog. Coord., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 14-16—**Medicine and the Changing World.** Vista Hill Foundation at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Virginia Everett, Vista Hill Fnd., 7798 Starling Dr., San Diego 92123. (714) 278-6761.

February 24-26—**Neurology for Non-Neurologists.** UCSD at Hilton, San Diego. Sunday-Tuesday. 21 hrs. $250.

February 25-29—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $290.

February 26-March 2—**Critical Care Medicine.** USC at Hilton, San Francisco. Tuesday-Sunday.

February 27—**Hospital Infection Control.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday. 7 hrs. Contact: Prog. Coord., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland, OR 97227. (503) 280-3200.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

February 25-29—**Eleventh Annual Family Practice Review.** Portland, Monday-Friday. Marriott Hotel. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OBSTETRICS AND GYNECOLOGY

October 22-24—**Third Annual Pacific Northwest Review of Obstetrics and Gynecology.** Portland, Monday-Wednesday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

SURGERY

December 7-8—**Recent Advances in Surgery.** Portland, Friday-Saturday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OF INTEREST TO ALL PHYSICIANS

September 14-15—**Newer Concepts in Cardiology.** Ashland, Friday-Saturday. Ashland Hills Motel. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Edu-

cation, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

September 28-29—**Second Annual Paul Thornton Shaw Memorial Lectures in Geriatric Medicine.** Portland, Friday-Saturday. OMA Headquarters. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

October 4-5—**Understanding Human Sexuality: Current Assessment and Treatment Approaches.** Portland, Thursday-Friday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

November 16-17—**Sixth Annual Symposium on Critical Care Medicine.** Portland, Friday-Saturday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

January 25-27—**Seminars in Cardiology.** Portland, Friday-Sunday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 16-20—**American College of Physicians Review Course.** Portland, Monday-Friday. Jantzen Beach Thunderbird. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 25-27—**Symposium on Sports Medicine.** Eugene, Wednesday-Friday. Thunderbird Motor Inn. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association. 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

September 17-21—**Advances in Family Practice.** Seattle. Monday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

September 20-23—**Radiology Northwest III.** Seattle. Thursday-Sunday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

September 23-24—**Medical Problems in the Surgical Patient.** Walla Walla. Sunday-Tuesday. Walla Walla General Hospital. Contact: Sharon Werner, Walla Walla General Hospital, 933 Bonsella, Walla Walla, WA 99362. (509) 522-0480, Ext. 543.

September 27-29—**Plastic Surgery Repair for Primary MDs.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

September 29—**Third Annual Cancer Symposium: Current Concepts in the Management of Colon Cancer.** Tacoma. Saturday. Tacoma General Hospital Medical Building Auditorium. Contact: Mary Faulk, Department of Oncology, Tacoma General Hospital, 315 South "K" Street, Tacoma, WA 98405. (206) 597-6964.

October 4-5—**Immediate Care of the Sick and Injured.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050

October 5-6—**Scientific Program, Annual Meeting, Washington State Medical Association.** Seattle. Friday-Saturday. Washington Plaza Hotel. Contact: Mr. George Morford, Washington State Medical Association, 2033 Sixth Avenue, Seattle, WA. (206) 623-4801.

October 8-19—**Echocardiography.** Seattle. Two weeks. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

October 11-12—**Advanced Exercise Testing.** Seattle. Thursday-Friday. Safeco Plaza. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

October 11-12—**Office Gynecology for Primary MDs.** Seattle. Thursday-Friday. U/W Child Development and Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

October 18-19—**Thyroid Disorders and Treatment.** Port Ludlow. Thursday-Friday. Port Ludlow Resort. Contact: Marlyn Carlson, Northwest Hospital, 1551 North 120th, Seattle, WA 98133. (206) 364-0500, ext. 686.

October 19-20—**Nutrition for Physicians.** Seattle. Friday-Saturday. U/W Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

November 1-2—**Drug Therapy.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

November 4-7—**Twenty-Two Postgraduate Courses.** Las Vegas, Nevada. Sunday thru Wednesday. Contact: AMA Department of Meeting Services, 535 North Dearborn Street, Chicago, Illinois 60610.

November 8-9—**Basic Psychotherapeutic Techniques.** Seattle. Thursday-Friday. Swedish Hospital Auditorium. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

November 15-16—**Critically Ill Surgical Patient.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

November 17-24—**Tax Estate and Financial Planning.** Kauai, Hawaii. Saturday thru Saturday. Kauai Surf. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

November 30, December 1—**Aging and the Elderly.** Seattle. Friday-Saturday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

December 6-7—**American College of Physicians MKSAP V.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

December 6—**Behavioral Methods in Pain Management.** Seattle. Thursday. Swedish Hospital Auditorium. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

December 7—**Biofeedback.** Seattle. Friday. Swedish Hospital Auditorium. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

January 17-18—**Pediatric Update.** Seattle. Thursday-Friday. Children's Orthopedic Hospital and Medical Center. Contact: UW School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

January 29-30—**Tax Estate and Financial Planning.** Seattle. Tuesday-Wednesday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 1-2—**Violence in the Family.** Seattle. Friday-Saturday. Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 9-16—**Sun Valley Critical Care: Maternal/Perinatal.** Sun Valley, Idaho. Saturday thru Saturday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: 1980—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 23-27, 1980, Registry Resort, Scottsdale.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: February 7-13, 1980, Town and Country, San Diego.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 19-23, 1979, the Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 8-12, 1979, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual meeting: 1980—date and place to be announced.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 11-13, 1979, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 16-18, 1980, MGM Grand, Las Vegas.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: 1980—date and place to be announced.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Meeting: November 2-4, 1979, OMA Headquarters.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: 1980—date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 4-7, 1979, Washington Plaza Hotel, Seattle.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: 1980—date and place to be announced.

February 14-15—**Advances in Neurology: Headaches.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 28-29—**Northwest Stroke Symposium.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: Education and Training Department, Northwest Hospital, 1551 North 120th, Seattle, WA 98133. (206) 364-0500, ext. 686.

April 25-26—**Anesthesia: Low Flow States—Pathology and Treatment.** Vancouver, British Columbia. Friday-Saturday. Four Seasons Hotel. Contact: Dr. K. Turnbull, Academy of Medicine, 1807 West 10th Avenue, Vancouver, BC V6J 2A9.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

MONTANA

October 5-6—**American Cancer Society (Montana Chapter) Annual Meeting.** Billings. Friday-Saturday. Northern Hotel. Contact: Ruth Eaton, 2820 1st Ave. S., Billings, MT 59101.

October 11-13—**Montana Medical Association Annual Meeting.** Kalispell. Thursday-Saturday. Outlaw Inn. Contact: Montana Medical Association, 2021 Eleventh Ave., Suite 12, Helena, MT 59601. (406) 443-4000.

IDAHO

February 9-16—**Sun Valley Critical Care: Maternal/Perinatal.** Sun Valley, Idaho. Saturday thru Saturday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

Index to
The Western Journal of Medicine Advertising

BANK OF AMERICA
Business Services 15
BURROUGHS WELLCOME CO.
Neosporin 17
CLASSIFIED 24, 25, 26
DOCTORS' COMPANY, THE 14
ELI LILLY AND COMPANY
Keflex 3
ENDO LABORATORIES
Percocet-5 ..... 12, 13
FIRSTMARK CAPITAL CORPORATION 7
HOLY CROSS HOSPITAL
New-Sleep Disorders Center 7
HOSPITAL OF THE GOOD SAMARITAN, L.A.
Symposium—Diabetes Mellitus 22
MEAD JOHNSON PHARMACEUTICAL DIVISION
Vasodilan 16
MERCK SHARP & DOHME
Aldomet 12
NORTHRIDGE HOSPITAL MEDICAL CENTER
2nd Annual—Heart Symposium 27
OBETROL PHARMACEUTICALS
Obetrol 18
OREGON MEDICAL ASSOCIATION
2nd Annual Paul Thornton Shaw
Memorial Lectures-Geriatric Medicine 23
PACIFIC MEDICAL CENTER
Course Offerings August-December, 1979 31
PHARMACEUTICAL MANUFACTURERS ASSOCIATION 20, 21
PHYSICIANS & SURGEONS INSURANCE EXCHANGE 10
PRESTO FOOD PRODUCTS, INC.
Mocha Mix 11
PUREPAC PHARMACEUTICAL CO. 19
RETIREMENT SYSTEMS INC. 23
ROCHE LABORATORIES
Librax ..... 2nd Cover, 1, 2
Valium ..... 3rd & 4th Covers
SANDOZ PHARMACEUTICALS
Hydergine 8
SMITH KLINE & FRENCH COMPANY
Tagamet 9
E. R. SQUIBB & SONS, INC.
Halog 5, 6, 7
U.S. ARMY RECRUITING 31

THE WESTERN Journal of Medicine

VOLUME 131 • NUMBER 4 **OCTOBER 1979**

263 *Epidemiologic Clues to the Cause of Melanoma*
WILLIAM E. MORTON, MD, DrPH, and GRIER F. STARR, MD

270 *Hypoglycemic Coma With Ketoacidosis in Nondiabetic Alcoholics*
EDWARD V. PLATIA, MD, and T. H. HSU, MD

277 *Mannitol* ALLEN R. NISSENSON, MD; RAYMOND E. WESTON, MD, and CHARLES R. KLEEMAN, MD

MEDICAL PROGRESS
285 *Diseases of Phenylalanine Metabolism* CHARLES E. PARKER, MD

SPECIALTY CONFERENCE
298 *Hypoparathyroidism*
Participants: KENNETH LEE JONES, MD; JAMES MURPHY, MD, and WILLIAM L. NYHAN, MD, PhD
Department of Pediatrics, University of California, San Diego, School of Medicine, the University of California Medical Center, San Diego, and the United States Naval Regional Medical Center, San Diego

MEDICAL STAFF CONFERENCE
305 *Vitamin D Deficient States—Pathophysiology and Treatment* Chief Discussant: MARK D. JACOBS, MD

IMPORTANT ADVANCES IN CLINICAL MEDICINE
313 *Allergy—Epitomes of Progress*

EDITORIALS
321 • *Alcoholic Hypoglycemia and Ketosis* • *Nationalized Health Care—A Juggernaut in 1981*
• *Phenylketonuria and Its Variants*

CASE REPORT
327 *Serious Infectious Complications After Flexible Fiberoptic Bronchoscopy*
YOSSEF AELONY, MD, and SYDNEY M. FINEGOLD, MD

CORRESPONDENCE
334 • *On Smoking and Advertising; With Reply by Author* • *Exercise and Neuromuscular Disease*
• *Toxicity of the Herbicide 2,4,5-T* • *Human Intestinal Parasites in a Farm Community*
• *Treatment of Gonococcal Pharyngeal Infections in Men*

PUBLIC HEALTH
339 *Bacterial Meningitis in Washington State* PAUL R. OSTROY, MD

HEALTH CARE DELIVERY
344 *Cardiopulmonary Resuscitation in a University Hospital—An Analysis of Survival and Cost*
RICARDO G. HAHN, MD; JOHN C. HUTCHINSON, MD, and JOHN E. CONTE, JR, MD

INFORMATION
349 *Shigellosis in Adults—Diagnostic Difficulties and Delays* JAY A. JACOBSON, MD

353 *Book Reviews* • *Books Received, See Advertising Page 21*

354 *In Memoriam*

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII; OREGON; WASHINGTON; ALASKA, MONTANA AND IDAHO**
(See Advertising Page 36)

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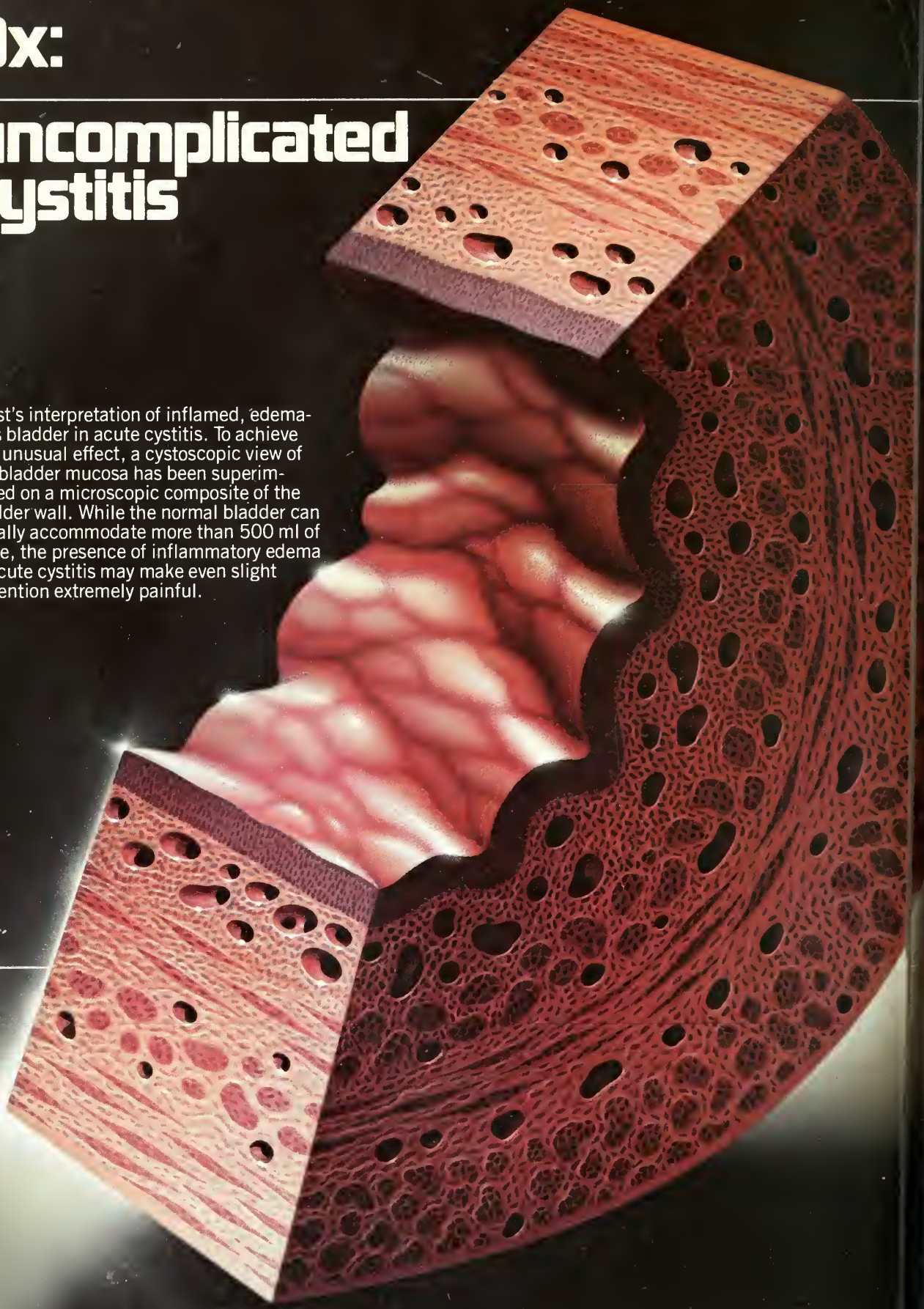

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Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

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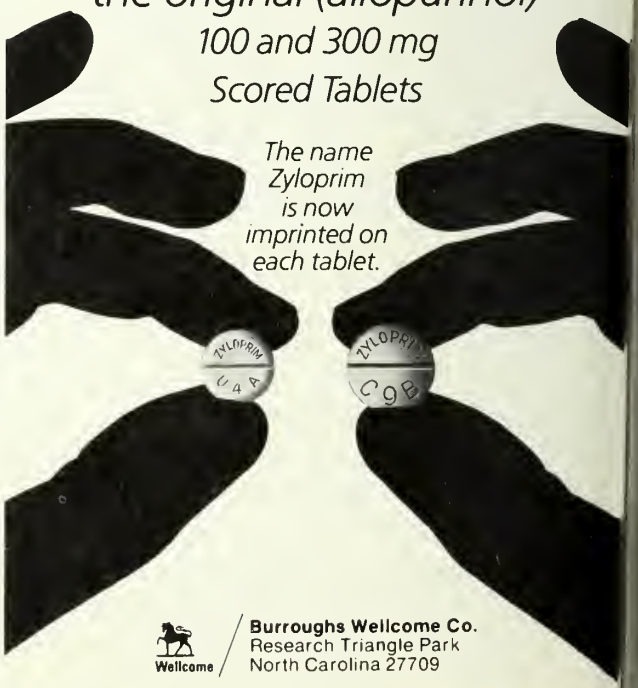

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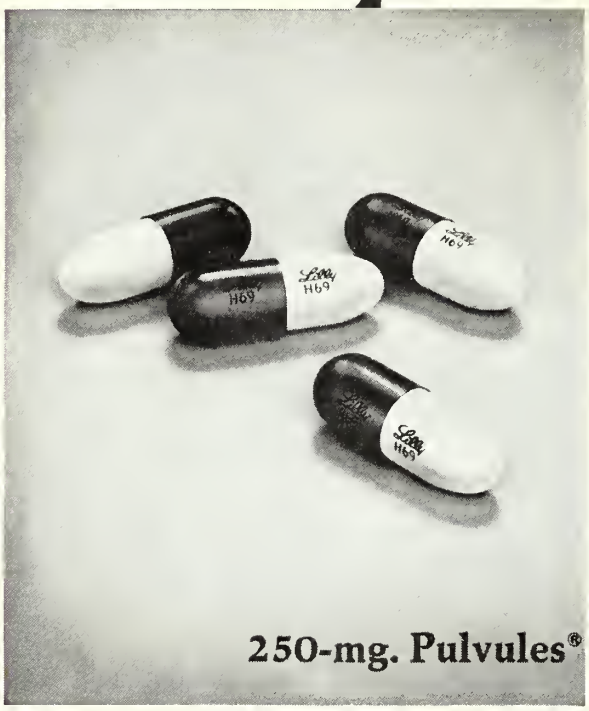

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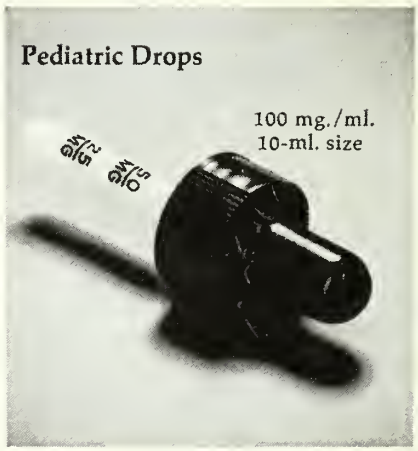

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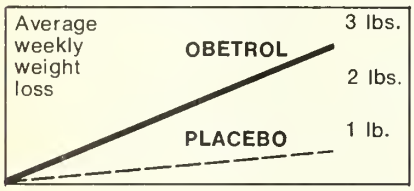

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Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
   a. Not recommended for children under 3 years of age.
   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, once or twice daily, increased in increments of 5 milligrams at weekly intervals. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

Availability: Supplied in bottles of 100; 500 and 1,000 tablets.

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January 1973

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Ventricular hypertrophy	Hepatic disease
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Bronchial asthma	Sulfonamide hypersensitivity

Like any antihypertensive, use with caution in severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

work/play—normal hemodynamic responses to exercise maintained.

love—low incidence of impotence and/or loss of libido: 2.8% in 1,923 patients studied.[1]

cardiac output—tends to return to control values during long-term therapy.

blood flow—preserved in kidney.

No Single Advantage Determines Drug Choice.

Other factors must include:

The drug's effectiveness in a given patient, its side effects, warnings, precautions, tolerance, etc. A rational therapeutic choice depends on a careful assessment of all such factors.

*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

1 Data on file at Boehringer Ingelheim Ltd.

Please see last page for brief summary, including warnings, precautions, and adverse reactions.

Tablets of 0.1 mg and 0.2 mg

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(clonidine HCl)

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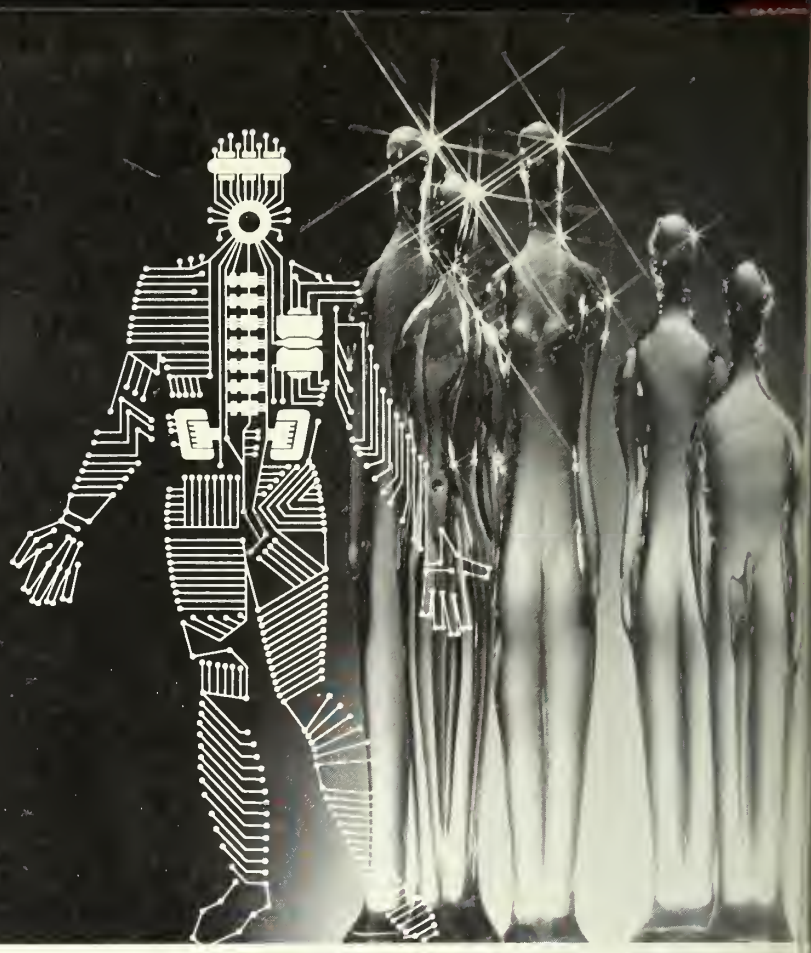

- No contraindications.
- Effective in all degrees of hypertension. It is mild to moderate in potency.
- Low incidence of depression, impotence, orthostatic hypotension—no fatal hepatotoxicity.
- Preserves kidney blood flow.

Most common side effects are dry mouth, drowsiness, and sedation which generally tend to diminish with time.

The usual starting dose of Catapres is 0.1 mg at breakfast and 0.1 mg at bedtime. Some patients may benefit from a starting dose of 0.1 mg at bedtime.

Usual daily dose range—0.2—0.8 mg

Maximum daily dose—2.4 mg (12 tablets of 0.2 mg). Doses as high as this have rarely been employed.

For optimal results, the dose of Catapres must be adjusted according to the patient's individual blood pressure response.

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 mo[illegible] longer.

Adverse Reactions: The most common reactions are dry mouth, drowsine[illegible] sedation. Constipation, dizziness, headache, and fatigue have been re[illegible] Generally these effects tend to diminish with continued therapy. The fo[illegible] reactions have been associated with the drug, some of them rarely. (In [illegible] instances an exact causal relationship has not been established.) These i[illegible] Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnorma[illegible] liver function tests; one report of possible drug-induced hepatitis without [illegible] and hyperbilirubinemia in a patient receiving clonidine hydrochloride [illegible] thalidone and papaverine hydrochloride. Weight gain, transient elevation [illegible] glucose, or serum creatine phosphokinase: congestive heart failure, Ray[illegible] phenomenon; vivid dreams or nightmares, insomnia, other behavioral ch[illegible] nervousness, restlessness, anxiety and mental depression. Also ra[illegible] gioneurotic edema, hives, urticaria, thinning of the hair, pruritus not ass[illegible] with a rash, impotence, urinary retention, increased sensitivity to alcohol, d[illegible] itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecom[illegible] weakly positive Coombs' test, asymptomatic electrocardiographic abnor[illegible] manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminishe[illegible] sent reflexes and vomiting followed the accidental ingestion of Catapres (c[illegible] hydrochloride) by several children from 19 months to 5 years of age. [illegible] lavage and administration of an analeptic and vasopressor led to comp[illegible] covery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30 [illegible] intervals usually abolishes all effects of Catapres, (clonidine hydrochlorid[illegible] dosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available a[illegible] (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 an[illegible]
For complete details, please see full prescribing information.
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The Upjohn Company announces a new indication for Motrin®
(ibuprofen)

A well-tolerated, nonnarcotic prescription for pain

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Motrin now proved an effective analgesic for mild to moderate pain

Motrin 400 mg provided greater relief of pain than did propoxyphene 65 mg in controlled clinical pain studies.

Time after drug administration (hour)		.5	1	2	3	4
Mean relief-of-pain scores* (No. patients reporting)	Motrin 400 mg ibuprofen	.89 (108)	1.25 (108)	1.36 (108)	1.28 (107)	1.19 (106)
	Darvon 65 mg propoxyphene	.66 (100)	.99 (99)	1.13 (96)	.99 (96)	.80 (96)
Statistical significance		$p<0.02$	$p<0.01$	$p<0.05$	$p<0.02$	$p<0.002$

*0 = No relief 1 = Partial relief 2 = Complete relief

Data on file at The Upjohn Company

Motrin demonstrated statistically significant greater relief of pain than did Darvon at all time intervals.

Motrin 400 mg TABLETS
ibuprofen, Upjohn

- Not a narcotic • Not addictive • Not habit forming
- Rapid analgesic action • Indicated in acute and chronic pain
- Well tolerated. The most common side effect with Motrin is mild gastrointestinal disturbance.

Please turn the page for a brief summary of prescribing information.

Upjohn

Motrin® (ibuprofen) now proved an effective analgesic for mild to moderate pain

Motrin® Tablets (ibuprofen, Upjohn)

Indications and Usage: Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Relief of mild to moderate pain.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin*. used concomitantly may decrease Motrin blood levels. *Coumarin*: Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy or by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin is gastrointestinal (4% to 16%). This includes nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness,* headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

*Incidence 3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine, so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid and osteoarthritis, including flares of chronic disease: Suggested dosage is 300, 400 or 600 mg t.i.d. or q.i.d.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for relief of pain.

Do not exceed 2400 mg per day.

Caution: Federal law prohibits dispensing without prescription.

For additional product information, see your Upjohn representative or consult the package insert.

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J-7280-4 August, 1979

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THE WESTERN
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Refer to: Morton WE, Starr GF: Epidemiologic clues to the cause of melanoma. West J Med 131:263-269, Oct 1979

Epidemiologic Clues to the Cause of Melanoma

WILLIAM E. MORTON, MD, DrPH, *Portland, Oregon,* and
GRIER F. STARR, MD, *Eugene, Oregon*

An intensive search found that 146 cases of cutaneous or ocular melanoma had occurred among residents of Lane County, Oregon, from 1958 through 1972. Of these cases, 35 led to death. Countywide, increasing incidence rates were corroborated by increasing death rates for both sexes. Risk of disease was highest in a moist, flat residential area near the intersection of two rivers in the county's urban portion and in its agricultural area. The incidence pattern strongly suggested local cycles in subcounty units. Although overall melanoma risk was higher in urban areas, an apparent widespread rural epidemic was identified, beginning abruptly in 1965 and lasting several years. If similar geographic and temporal characteristics can be identified in other localities, the search for an etiologic agent could focus on a smaller range of possibilities.

ALTHOUGH THE CAUSE of melanoma remains to be clarified, it probably is multifactorial in nature. Possible etiologic factors can be grouped into categories: microbiologic (viruses, mycotoxins), chemical (inorganic, organic), radiation (ionizing, perhaps nonionizing) and genetic abnormality (viral genomes, mutations), all of which may interact.[1,2] The heritable component (susceptibility) of melanoma causation is represented by the relative immunity enjoyed by darkly pigmented persons[2,3] and by the occurrence of families with a strong multigenerational pattern of involvement.[4-6] The wide variations reported for the occurrence of melanoma in different parts of the world have drawn attention to the likelihood that environmental factors are important influences in its geographical distribution. There is general agreement that exposure to solar radiation is another important risk factor for melanoma incidence,[2,3,8-11] leading to an observed inverse correlation with latitude of residence.

Of considerable concern are the reports of increasing incidence of melanoma and mortality in California and other states, Canada, western Europe and Australia.[12-16] Lee and other investigators have ascribed this increase largely to a modern tendency to wear fewer clothes, thereby risking greater exposure to solar radiation,[8,10,11,17] although MacDonald has presented data from Texas that show higher melanoma rates in more

From the Environmental Medicine Division, University of Oregon Medical School, Portland (Dr. Morton), and the Department of Pathology, Sacred Heart Hospital, Eugene, Oregon (Dr. Starr).

Supported by a grant from the Oregon State University, Environmental Health Science Center, headed by Dr. Virgil Freed.

Submitted, revised, May 24, 1979.

Reprint requests to: William E. Morton, MD, DrPH, Environmental Medicine Division, University of Oregon Medical School, Portland, OR 97201

humid communities with fewer sunny days.[18] Unfortunately, the designation *sunny day* is not an adequate measure of solar exposure, but adequate measurements are not generally available for intrastate comparisons. In Finland, Teppo and colleagues found that the typical north/south gradient in melanoma incidence was obliterated if the data were adjusted for degree of urbanization.[19] It seems reasonable to entertain other hypotheses besides greater exposure to solar radiation to account for increased melanoma incidence.

Suspicions of the potential role of chemical carcinogens are beginning to appear in the literature. Bahn and co-workers reported the development of melanoma in two men with occupational exposure to polychlorinated biphenyls;[20,21] Albert and Puliafito reported two cases of ocular melanoma in a group of Ohio Valley chemical workers exposed to hydrazine and dimethylsulfate.[22] Certain workers in steel and nonferrous metals industries also seemed at excessive risk.[23] Therefore, increased melanoma risk in persons with greater outdoor exposure[24,25] may be due to solar radiation exposure, to greater environmental chemical exposure or to an interaction between the two.

Using 15-year mean annual mortality rates for Oregon, Figure 1 shows that high-risk counties are scattered almost randomly across the state except for a cluster of counties in the southwestern corner. Because most of its population lives in the western third of Oregon, this southwestern cluster of counties with high melanoma mortality agrees with the national pattern of higher mortality in lower latitudes as reported by Mason and colleagues.[26] However, we do not propose that latitude alone fully explains the high melanoma mortality in southwestern Oregon. The melanoma mortality for Lane County, Oregon's second largest metropolitan area, was entirely unremarkable and below the statewide average, but an opportunity to study the local distribution of this disease arose in the course of a study of skin cancer incidence in relation to water arsenic levels.[27] The spatiotemporal characteristics of melanoma were sufficiently unique to warrant separate description.

Methods

For this study, the primary data sources, like those of the Third National Cancer Survey,[28] were pathology files. All six hospitals in Lane County were served by a single group of pathologists whose files were scanned for cases of melanomas and other skin tumors for the years 1958 through 1972. We also sought Lane County cases from the pathologist in Coos Bay who periodically served coastal portions of Lane County, and from a mail-order private pathology laboratory

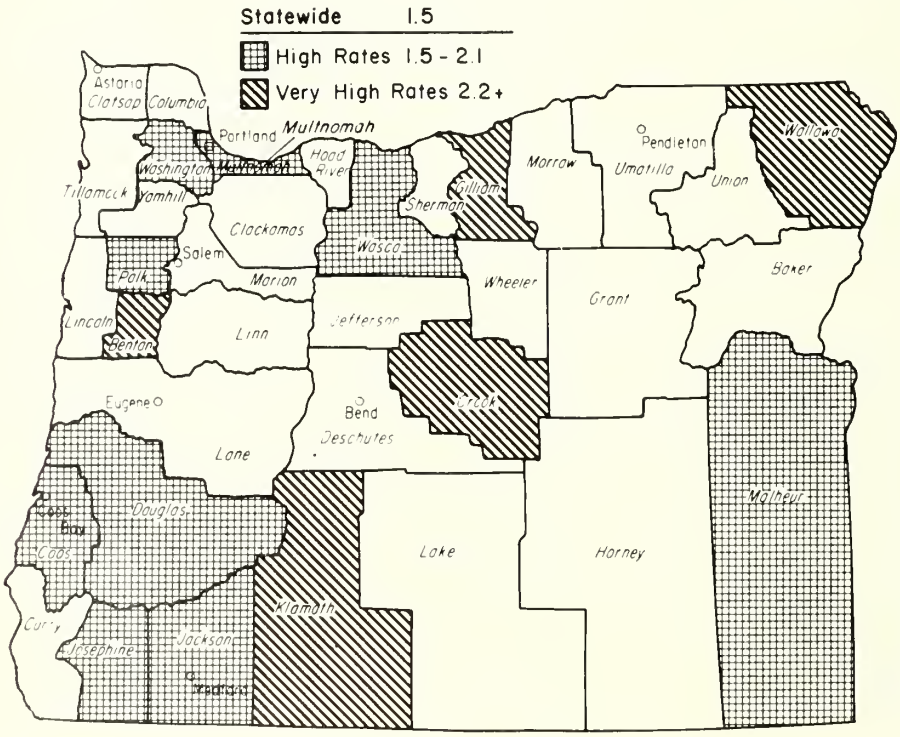

Figure 1.—Melanoma mortality in Oregon between 1958 and 1972. Mean annual age-standardized rates per 100,000.

TABLE 1.—*Trends in Melanoma Incidence and Mortality in Lane County, Oregon, Between 1958 and 1972**

Period	Incidence			Mortality		
	Males	Females	Both Sexes	Males	Females	Both Sexes
1958-1962 ...	3.2	4.0	3.6	0.9	0.0	0.4
1963-1967 ...	5.6	5.2	5.3	2.5	0.5	1.4
1968-1972 ...	7.7	6.8	7.2	2.4	1.8	2.1
Total 1958-1972	5.7	5.4	5.5	1.9	0.9	1.4
(cases)[deaths]	(71)	(75)	(146)	[23]	[12]	[35]

*Mean annual age-standardized rates per 100,000.

TABLE 2.—*Age Distribution by Gender of Melanoma Incidence and Mortality in Lane County, Oregon, Between 1958 and 1972**

Age (Years)	Incidence			Mortality		
	Males	Females	Both	Males	Females	Both
0-14	0.0	0.0	0.0	0.0	0.0	0.0
15-24	2.0	2.7	2.3	0.0	0.0	0.0
25-34	2.7	5.4	4.0	0.0	0.0	0.0
35-44	9.0	10.0	9.5	3.0	1.8	2.4
45-54	5.8	9.7	7.7	2.6	0.7	1.6
55-64	11.3	8.8	10.2	4.3	3.6	3.9
65-74	19.1	14.3	16.6	2.9	3.9	3.5
75-84	33.2	13.1	22.0	23.4	2.8	11.7
85+	14.4	0.0	6.0	0.0	0.0	0.0
Rate for All Ages† ..	5.7	5.4	5.5	1.9	0.9	1.4
Total	71	75	146	23	12	35

*Mean annual age-specific crude rates per 100,000.
†Standardized to the age distribution of the 1970 United States population.

in Portland, from the Veterans Administration Hospital tumor registry in Portland and from the University of Oregon Medical School tumor registry in Portland. The large and diverse medical community in Eugene has been a medical referral center for the surrounding largely rural counties for many years, so that very few persons go elsewhere for diagnosis and therapy. Ocular melanomas were added to our data because it did not seem logical to exclude a single anatomic site of an uncommon disease. Mortality experience also was reviewed for Lane County residents who died of cutaneous or ocular melanoma during these 15 years.

For geographic analysis, cases were assigned to the census tract of residence at the time of diagnosis or at time of death, respectively. Census tracts were grouped into geographic regions or socioeconomic strata, the latter according to a scoring system based on median family income, proportion of families below the poverty level, adult education attainment and household crowding (code available on request). For risk estimation we used mean annual rates standardized by the direct method to the age distribution of the

TABLE 3.—*Geographic Distribution by Gender of Melanoma Incidence and Mortality in Lane County, Oregon, Between 1958 and 1972**

Geographic Region	Incidence			Mortality		
	Males	Females	Both	Males	Females	Both
Rural (Subtotal) .	5.9	3.5	4.8	2.2	0.7	1.4
North	9.2	4.7	6.8	3.1	0.0	1.6
East	5.6	3.5	4.6	1.7	1.0	1.3
South	4.5	2.0	3.3	2.9	0.0	1.4
Midwest	7.4	2.8	5.2	1.4	0.0	0.7
Coast	4.1	6.8	5.4	1.7	3.4†	2.5
Urban (Subtotal).	5.4	6.4	5.9	1.7	1.0	1.3
NE Springfield	4.4	10.6†	7.4	0.0	4.8‡	2.3
SW Springfield	5.9	4.6	5.2	3.7	0.0	1.7
S Eugene	5.3	4.7	5.0	0.5	1.0	0.8
W Eugene	4.0	8.3	6.2	2.7	1.3	2.0
NW Eugene ..	6.7	5.4	6.0	2.4	0.7	1.2
N Eugene	9.0	14.3‡	11.8‡	2.1	1.6	1.8
Core Eugene .	3.6	3.3	3.4	1.5	0.6	1.0
Lane County Total	5.7	5.4	5.5	1.9	0.9	1.4

*Mean annual age-standardized rates per 100,000.
†P<.05 } Significance of difference from respective county rate.
‡P<.01 }

population of the United States in 1970. For statistical judgment of comparisons of regional rates with the countrywide rate we used the statistic Z, equal to the rate difference $(\overline{X}_0 - \overline{X}_1)$ divided by the square root of $\overline{X}_0(B - X_0)\ (1/N_0 + 1/N_1)\ 1/T$; where B is the rate base used, $\overline{X}_1$ is the regional rate being tested, $\overline{X}_0$ is the respective countywide rate, N_1 and N_0 are the mean or median populations from which $\overline{X}_1$ and $\overline{X}_0$ were calculated, and T is the number of years included in the mean annual rate.

Results

Table 1 shows that during this 15-year period, 146 new cases of melanoma were diagnosed in Lane County (5.5 per 100,000 per year), and 35 deaths resulted from melanoma (1.4 per 100,000 per year). According to these data, both sexes showed increasing incidence and mortality, with the exception of male mortality between 1968 and 1972. Men had consistently greater mortality and often had higher incidence rates as well. The total melanoma incidence rates in Lane County for 1968 to 1972 were higher than the 1969 to 1971 Third National Cancer Survey's cutaneous melanoma incidence rates by 67.4 percent for men and 54.5 percent for women,[28] an excess that cannot be accounted for by the 4 percent of Lane County cases that were ocular melanomas. There were no melanoma cases or deaths among nonwhites, who make up only a small fraction of the population (0.72 percent

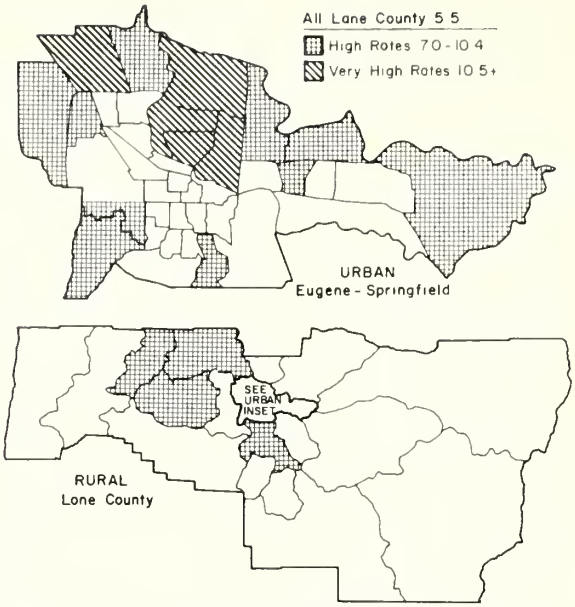

Figure 2.—Melanoma incidence in Lane County, Oregon, between 1958 and 1972. Mean annual age-standardized rates per 100,000.

in 1960 and 1.45 percent in 1970), so that racial distribution patterns did not affect our observations.

Table 2 illustrates the effect of age. Both sexes showed bimodal age distributions for both melanoma indices, with secondary peaks for the 35 to 44 year age stratum, but with maximum rates at ages 75 to 84 years for men and 65 to 74 years for women. Incidence rates were slightly higher among women than men at ages 15 to 54 years and higher among men than women 55 years old or older. The greater total male mortality was due almost entirely to a very high death rate in men aged 75 to 84 years (seven deaths). Age at diagnosis ranged from 15 to 89 years, while age at death varied from 35 to 83 years.

Table 3 presents the geographic regional distribution of melanoma occurrence and mortality. The range of incidence rates was greater for women (2.0 to 14.3) than for men (3.6 to 9.2), which reflects classification by place of residence. This geographical distribution would be expected to be more accurate for women than for men on the average (due to lesser influence of occupational confounding) and is compatible with the hypothesis that place of residence influences melanoma risk. The contiguous urban regions of north Eugene and northeast Springfield seemed to warrant suspicion of high melanoma risk because north Eugene had significantly elevated incidence

TABLE 4.—*Socioeconomic Distribution by Gender of Melanoma Incidence and Mortality in Lane County, Oregon, Between 1958 and 1972**

Socioeconomic Score†		*Incidence*			*Mortality*		
		Males	*Females*	*Both*	*Males*	*Females*	*Both*
High	20-39	8.8	4.3	6.4	0.0	2.2	1.2
	40-49	6.5	10.2	8.5	1.2	1.4	1.3
	50-59	3.8	7.2	5.5	1.0	0.7	0.8
	60-69	4.9	4.9	4.9	2.7	0.8	1.7
	70-79	6.7	3.5	5.1	2.3	1.0	1.6
Low	80-89	2.8	1.9	2.5	0.0	0.0	0.0
Total		5.7	5.4	5.5	1.9	0.9	1.4

*Mean annual age-standardized rates per 100,000.
†Sum of unweighted scores for 1970 census variables:
- family income
- percent of families with income below poverty level
- adult education attainment
- household crowding

rates for women and for both sexes combined, and because northeast Springfield had significant elevations of both incidence and mortality among women.

Figure 2 shows the distribution by individual census tracts for melanoma incidence in both sexes combined, which was very high (10.5 or more) in a group of five census tracts in north and northwest Eugene. The peak rate of 12.0 occurred in two adjacent census tracts, the larger of which lies at the confluence of the McKenzie and Willamette Rivers. In the urban tracts, those with merely high rates (7.0 to 10.4) tended to cluster in the flat, moist bottom land adjacent to the peak-risk tracts, while rural high-risk census tracts included the major part of the agricultural land in Lane County bordering on Benton County (whose high-risk status was evident in Figure 1). According to the Sanitation Division of the Lane County Health Department, the high-risk melanoma region along the northern edge of both Eugene and Springfield has also been the region where the most active mosquito control efforts in the county have been required. From 1950 to 1963 DDT was the primary insecticide; since 1963 malathion and fenthion have been used. One might suspect DDT exposure as potentially important, given a recent report of excessive melanoma risk after exposure to polychlorinated biphenyls.[20,21]

The overall socioeconomic distributions of melanoma incidence and deaths are given in Table 4. Mortality in women showed the strongest tendency for a direct association with socioeconomic status. The same tendency for a positive correlation with socioeconomic status appeared in the incidence data, where it was manifested by

both sexes, although less consistently. The effect of socioeconomic status on melanoma distribution seemed to be relatively weaker and more inconsistent than the geographic pattern, and neither effect was influenced by the proportion of dark-skinned persons in the population (as judged by proportion of blacks by census tract).[29]

In Table 5 the melanoma cases were regrouped into four sets of rates rather than three because this temporal grouping showed more distinctly the onset of a rural epidemic of melanoma incidence that began in 1965. This phenomenon could not be accounted for by any change in diagnostic criteria or change in membership of the pathology group, nor by change in hospital service pattern of the pathologists, so that it is interpreted as a predominately rural epidemic in which the urban west, northwest and north Eugene regions also participated. Just before the 1965 outbreak, melanoma incidence had declined in most parts of the county, producing a strong impression of cyclical incidence pattern. Although division of the total time span into four shorter periods lessened the likelihood of recognizing significant local deviations from the respective countywide incidence rates, scattered significant deviations were evident (Table 5). In only one region, north Eugene, did the local rate consistently exceed the countywide rate during all four time periods, corroborating the earlier impressions about this region given in Table 3 and Figure 2. The rural north showed two incidence peaks of about the same magnitude occurring about a decade apart. Other small outbreaks took place in Springfield between 1962 and 1964, and on the coast between 1969 and 1972.

After studying the geographic and temporal variations observed in melanoma incidence, it was natural to wonder if there existed a seasonal pattern of occurrence, as approximated by the date of diagnosis. Table 6 shows the months of diagnosis by year and by gender. From 1958 to 1963 there appeared to be some grouping of cases during the sunny months of June through October; however, the subsequent years showed a general year-round pattern of occurrence. Overall, there were four to nine new cases of melanoma in men in any one month, and peak months were June and August; in women there were between one and ten cases appearing in any one month, and peak months were January and May. Therefore, there was a difference between sexes but no simple pattern for either. We need to compare

TABLE 5.—*Trends in Melanoma Incidence in Geographic Regions of Lane County, Oregon, Between 1958 and 1972**

Geographic Region	1958-1961	1962-1964	1965-1968	1969-1972
Rural (Subtotal)	2.2	0.6	6.4	7.5
North	10.2§	0.0	5.8	10.6
East	1.7	0.0	8.2	6.6
South	1.5	0.0	4.1	4.6
Midwest	0.0	3.1	6.5	7.9
Coast	0.0	0.0	6.5	12.2
Urban (Subtotal)	4.2	3.8	5.5	6.9
NE Springfield	4.5	12.4‡	4.7	5.7
SW Springfield	3.3	5.9	1.3	7.8
S Eugene	5.1	3.5	3.1	6.8
W Eugene	3.8	2.3	7.9	5.8
NW Eugene	0.0	0.0	11.0§	5.1
N Eugene	8.3	5.9	9.3	15.6†
Core Eugene	4.5	0.0	4.4	4.5
Lane County Total	3.5	2.7	5.8	7.1

*Mean annual rates per 100,000.
†P<.05, ‡P<.01, §P=.06 } Significance of difference from respective county rate.

TABLE 6.—*Month and Year of Initial Diagnosis of Melanoma Cases in Lane County, Oregon, Between 1958 and 1972*

Month of Diagnosis	*Year of Diagnosis* 1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971	1972	M	F	Both
Jan	.	1	1	1	.	2	.	.	.	2	1	3	1	1	2	5	10	15
Feb	1	.	.	.	.	.	1	1	1	.	1	.	2	1	2	7	3	10
Mar	.	1	.	.	.	.	1	1	2	2	1	2	.	1	3	6	8	14
Apr	.	1	.	.	.	.	1	2	.	1	1	1	.	3	1	4	7	11
May	1	.	.	.	.	.	.	1	.	2	4	1	1	3	2	4	11	15
Jun	.	.	1	3	.	2	1	1	1	2	1	1	2	1	1	9	8	17
Jul	.	.	.	.	.	.	.	1	4	2	1	.	1	2	1	5	7	12
Aug	2	2	.	2	.	1	.	.	1	1	.	2	1	2	2	9	7	16
Sep	1	.	1	2	.	1	.	.	.	.	1	2	2	2	1	8	5	13
Oct	.	.	.	.	2	1	1	.	.	3	.	.	.	1	2	5	5	10
Nov	1	.	.	.	.	.	.	1	.	1	1	1	1	1	1	5	3	8
Dec	.	1	.	.	1	.	.	1	1	.	.	.	1	.	.	4	1	5
Total	6	6	3	8	3	7	5	9	10	16	12	13	12	18	18	71	75	146

F = females; M = males.

the Lane County observations with those of other localities before deciding whether seasonal patterns should be suspected.

Discussion

Although solar radiation is undoubtedly a risk factor for the development of melanoma, it is unlikely that it is a sufficient explanation by itself because our data suggest that substantial temporal and spatial variations in incidence occur within a single geographic region whose solar radiation exposure is relatively uniform. Unfortunately, Lane County contains only one weather station, and no solar measurement data exist to permit intracounty comparisons to refine our inexact impressions. Curiously, the increasing incidence of melanoma in Lane County has occurred despite an overall trend of a declining mean number of clear days per year (92 in 1949 to 1952, 65 in 1973 to 1977) and of an increasing number of cloudy days (196 in 1949 to 1952, 223 in 1973 to 1977). More important, we seem to have identified in Lane County an area of high-risk for melanoma which has definite ecologic characteristics: suburban flat land with a high water table and a history of long-term, vigorous insect control measures. This disease distribution pattern may be related to insect vector distribution, to excessive human exposure to insect control measures, or to other characteristics that only happened to coincide with these variables. Investigations in other localities are imperative, and the use of census tracts seems to be a particularly valuable analytic method.

The temporal variations in melanoma incidence which we have interpreted as cycles or small epidemics might be called random fluctuation of small numbers by a skeptic. It is too soon to know which interpretation will prove correct, but it would be unwise to ignore the possibility of predictable cycles. The 15-year period of our study was long enough to identify a full cycle of incidence fluctuation in some, but not all, parts of the county. The impression of cyclic incidence suggested the likelihood of cycles of frequency of etiologic agents in the community, cycles that occurred within subcounty units. If cycles of similar periodicity could be identified in other communities, then one would tend to suspect a viral carcinogen as an explanation. Our epidemiologic findings agree with laboratory and clinical reports. Virus particles consistently have been found in tissue culture cell-lines from a transplantable melanoma of golden Syrian hamsters.[30] Nathanson has reported an incidence of verified spontaneous regression of melanoma five times greater than expected,[31] and Bulkley and coworkers have pointed out that the rare instances of spontaneous regression of melanoma have been associated with events suggesting the development of host immunity.[32] Several groups of investigators have been working with melanoma-associated antigens, and a recent report has suggested that delayed hypersensitivity to such antigens may be much more widespread than clinical melanoma,[33] a situation that occurs in a number of nonneoplastic granulomatous conditions. If a communicable agent is involved with the cause of melanoma, then it seems likely that its communicability is somewhat inefficient, that it tends to produce a chronic rather than an acute self-limiting infection and that reinfection must be a factor.

REFERENCES

1. Robbins SL: Pathologic Basis of Disease. Philadelphia, WB Saunders, 1974, pp 126-141
2. Norlund JJ, Lerner AB: On the causes of melanoma. Am J Pathol 89:443-448, Nov 1977
3. McGovern VJ, Lane Brown MM: The Nature of Melanoma. Springfield, IL, Charles C Thomas, 1969, pp 108-114
4. Turkington RW: Familial factor in malignant melanoma. JAMA 192:77-82, Apr 12, 1965
5. Kopf AW, Mintzis M, Brier WRN, et al: Familial malignant melanoma. Cutis 17:873-876, May 1976
6. Clark WH Jr, Reimer RR, Greene M, et al: Origin of familial malignant melanomas from heritable melanocytic lesions. Arch Dermatol 114:732-738, May 1978
7. Waterhouse JAH, Muir CS, Correa P, et al (Eds): Cancer Incidence in Five Continents, Vol 3. Lyon, France, IARC Scientific Publications, 1976, pp 508-511
8. Lee JAH: Sunlight and the etiology of malignant melanoma, *In* McCarthy WH (Ed): Melanoma and Skin Cancer. Sydney, Australia, Government Printer, 1972, pp 83-94
9. Elwood JM, Lee JAH, Walter SD, et al: Relationship of melanoma and other skin cancer mortality to latitude and ultraviolet radiation in the United States and Canada. Internat J Epidemiol 3:325-332, Dec 1974
10. Movshovitz M, Modan B: Role of sun exposure in the etiology of malignant melanoma—Epidemiologic inference. J Natl Cancer Inst 51:777-779, Sep 1973
11. Anaise D, Steinitz R, Ben Hur N: Solar radiation, a possible etiological factor in malignant melanoma in Israel. Cancer 42:299-304, Jul 1978
12. Lee AH, Carter AP: Secular trends in mortality from malignant melanoma. J Natl Cancer Inst 45:91-97, Jul 1970
13. Beardmore GL: The epidemiology of malignant melanoma in Australia, *In* McCarthy WH (Ed): Malignant Melanoma and Skin Cancer. Sydney, Australia, Government Printer, 1972, pp 39-64
14. Krain LS: Malignant melanoma of the skin in California, 1942-1969—Epidemiologic and survival considerations. Cutis 11: 350-357, Mar 1973
15. Elwood JM, Lee AH: Recent data on the epidemiology of malignant melanoma. Semin Oncol 2:149-154, Jun 1975
16. Epstein E, Bragg K: Changes in incidence of melanoma (Letter). Arch Dermatol 112:1174-1175, Aug 1976
17. Lee JAH, Yongchaiyudha S: Incidence of malignant melanoma by anatomical site. J Natl Cancer Inst 47:253-263, Jul 1971
18. Macdonald EJ: Epidemiology of melanoma, *In* Ariel IM (Ed): Progress in Clinical Cancer 6:139-149, 1975
19. Teppo L, Pakkanen M, Hakulinen T: Sunlight as a risk factor of malignant melanoma of the skin. Cancer 41:2018-2027, May 1978
20. Bahn AK, Rosenwaike I, Hermann N, et al: Melanoma after exposure to PCB's (Letter). N Engl J Med 295:450, Aug 19, 1976

21. Bahn AK, Grover P, Rosenwaike I, et al: PCB? and melanoma (Reply to Letter). N Engl J Med 296:108-109, Jan 13, 1977

22. Albert DM, Puliafito CA: Choroidal melanoma—Possible exposure to industrial toxin (Letter). N Engl J Med 296:634-635, Mar 17, 1977

23. Houten L: Increased risk of cancer among workers in metal-related occupations (abstract). Public Health Rep 91:569, Nov-Dec 1976

24. Gellin GA, Kopf AW, Garfinkel L: Malignant melanoma—A controlled study of possible associated factors. Arch Dermatol 99:43-48, Jan 1969

25. Paffenbarger RS Jr, Wing AL, Hyde RT: Characteristics in youth predictive of adult-onset malignant lymphomas, melanomas, and leukemias. J Natl Cancer Inst 60:89-92, Jan 1978

26. Mason TJ, McKay FW, Hoover R, et al: Atlas of Cancer Mortality for U.S. Counties, 1950-1969, DHEW Publication No. 75-780 (NIH). US Dept of Health, Education, and Welfare, 1975

27. Morton W, Starr G, Pohl D, et al: Skin cancer and water arsenic in Lane County, Oregon. Cancer 37:2523-2532, May 1976

28. Cutler SJ, Scotto J, Devesa SS, et al: Third National Cancer Survey—An overview of available information. J Natl Cancer Inst 53:1565-1575, Dec 1974

29. Census of Population and Housing 1970, Census Tracts. Final Report PHC(1)-64 Eugene, Oregon SMSA. US Bureau of the Census, 1972

30. Epstein WL, Fukuyama K: In-vitro culture of cloned hamster melanoma cells containing R-type virus. Cancer Res 33:825-831, Apr 1973

31. Nathanson L: Spontaneous regression of malignant melanoma—A review of the literature on incidence, clinical features and possible mechanisms. NCI Monograph 44, *In* Lewison EF (Ed): Conference on Spontaneous Regression of Cancer, DHEW Publication No. 76-1038(NIH). US Dept of Health, Education, and Welfare, 1976

32. Bulkley GB, Cohen MH, Banks PM, et al: Long-term spontaneous regression of malignant melanoma with visceral metastases. Cancer 36:485-494, Aug 1975

33. Char DH, Hollinshead A, Herberman RB: Skin tests with soluble melanoma antigens in patients with choroidal tumors. Cancer 40:1650-1654, Oct 1977

Refer to: Platia EV, Hsu TH: Hypoglycemic coma with ketoacidosis in nondiabetic alcoholics. West J Med 131:270-276, Oct 1979

Hypoglycemic Coma With Ketoacidosis in Nondiabetic Alcoholics

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Five nondiabetic, chronically alcoholic patients presented in a comatose state during a two month prospective study and were found to be ketoacidotic. All of the patients were men, 28 to 59 years old. The usual history was one of chronic heavy, daily alcohol consumption until one to three days before presentation, when persistent anorexia, abdominal distress, nausea and vomiting commenced, with abstention from food thereafter. The patients were found to be in hypoglycemic coma, with diaphoresis, tachypnea and tachycardia, and immediately awoke when intravenous infusion of glucose was started. Serum glucose ranged between 19 and 27 mg per dl, the average arterial pH was 7.19 and the mean anion gap was 25 mEq per liter. Reaction with Acetest tablets was positive for ketones in both serum and urine in three of the patients. Serum β-hydroxybutyrate was elevated in the four patients in whom it was measured. Lactic acidosis was not present.

All patients were managed with prolonged intravenous infusions of glucose and saline solutions, and within 12 to 18 hours they were feeling well and findings on serum chemistry studies were normal. Follow-up after three months showed no repeated difficulties. The combination of alcoholic ketoacidosis and hypoglycemic coma in nondiabetic persons has not been described in the literature as a clinical entity; it may, however, represent a common but unrecognized syndrome. Therefore, because of its potentially serious consequences and because treatment is simple and effective, this entity must be thought of in alcoholic patients with altered mental status.

HYPOGLYCEMIA induced by alcohol was first described by Brown and Harvey[1] in 1941 in six chronic alcoholic persons, but was felt for the next two decades to be secondary to congeners in alcoholic beverages. There have since been relatively few reported cases of alcohol-induced hypoglycemia—probably a significant underestimate of the incidence of this entity in chronic alcoholism.[2] Alcoholic ketoacidosis was first described by Dillon and associates[3] in 1940, but has only recently been further documented and investigated.[4-7] There are relatively few reports of this entity in the literature, but its occurrence may not be infrequent in cases of chronic alcoholism. With the exception of one report, more than three

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fourths of the reported cases have occurred in women; as a result, hormonal mechanisms have been proposed.[6]

The combination of alcohol-induced hypoglycemic coma occurring concomitantly with ketoacidosis, however, has not yet been described as a clinical entity, although a few such cases can be found included in previously published series.[4-7] We report five cases of hypoglycemic coma with ketoacidosis in nondiabetic alcoholic men. The clinical and laboratory findings, as well as possible causes and mechanisms, are described. This entity, we feel, is both important and not uncommon in cases of chronic alcoholism.

Methods

Each of the five patients presented to the Johns Hopkins Hospital emergency department and was seen by one of the authors (E.V.P.) over the space of two months, one a winter month (December) and the other a summer month (June). Except for one patient who was admitted to hospital, each remained in the emergency department less than 24 hours before leaving—either by discharge or against medical advice. All of the patients returned for follow-up evaluation. Blood chemistry, hematologic and arterial blood gas studies were done using routine hospital procedures. Arterial lactic acid levels were measured by a Dupont Automatic Clinical Analyzer, using the method of Marbach and Weil,[8] modified by Varley.[9] Serum β-hydroxybutyrate levels were measured using the principles outlined by Antonis and associates.[10] Serum insulin determinations were done using the radioimmunoassay technique of Morgan and Lazaran.[11] A *toxicology screen* (routine for all comatose patients in the emergency department) was done in each case; it includes qualitative urine and blood assays for the detection of alcohol, methanol, barbiturates, phenytoin, salicylate, glutethimide, meprobamate, chlordiazepoxide, diazepam, methaqualone, xanthines, phenothiazines, tricyclic antidepressants, opium alkaloids, synthetic narcotics, propoxyphene and amphetamines. Semiquantitative ketone determinations were done with Acetest tablets (Ames).

Reports of Cases

CASE 1. A 39-year-old man was brought to the emergency department one morning in a stuporous, semicomatose state, having been found at home in that state by a friend. He had been a regular, heavy drinker of alcohol for 22 years, but stopped drinking two to three days before because of lack of funds. He had not eaten for several days because of mild epigastric pain, nausea and vomiting. The patient later said he had not been exposed to toxins or taken drugs. There was no personal or family history of diabetes. The history was otherwise unremarkable.

On physical examination the patient had rapid, labored breathing and tachycardia. He was moderately diaphoretic with hepatomegaly and was minimally responsive to maximal verbal or pain stimulus. A study of blood using Dextrostix showed a low glucose level; therefore, thiamine was given intravenously, followed by 100 grams of glucose as a 50 percent dextrose solution. The patient immediately became alert and fully oriented and was able to give a coherent history, stating that the last thing he remembered was retiring to bed the previous night. The serum glucose level was 25 mg per dl and laboratory findings (Table 1) showed metabolic acidosis with weakly reactive Acetest test for ketones in serum; serum β-hydroxybutyrate was found to be greatly elevated (9.8 mEq per liter). Toxicology screen was negative. Glucose and saline solution was given intravenously, and within 12 hours arterial pH and blood chemistry values were normal, and the patient was discharged.

On follow-up at one month and three month intervals, continued alcohol ingestion was noted but no episodes similar to the earlier one had occurred. A glucose tolerance test was carried out and gave normal findings.

CASE 2. A 43-year-old man with a known history of chronic alcoholism was brought to the emergency room early one afternoon because he had lain in bed since morning in an unarousable state. He had stopped his usual daily intake of one quart of whiskey a day several days before, and had since then stopped eating regularly because of troublesome nausea and vomiting. There was no history of diabetes, nor any recent ingestion of toxins or drugs. The family history was negative for diabetes.

On physical examination the patient was comatose and afebrile, there were Kussmaul-type respirations and tachycardia, and blood pressure was minimally elevated. He was diaphoretic, with no acetone smell on his breath, and there was a grade II/VI systolic murmur and moderate hepatomegaly. He responded slightly to maximum noxious stimuli. Hypoglycemia was shown to be

present by Dextrostix. He was given 100 grams of glucose as 50 percent solution and awoke almost immediately, becoming fully alert and communicative. Results of laboratory studies are shown in Table 1 and included a glucose value of 21 mg per dl, with arterial pH of 7.18 and weakly reactive Acetest test for ketones in serum. Serum insulin was later found to be appropriately low, at 3 μU per ml. Dextrose and saline solution was given intravenously for 18 hours, and the patient left the hospital. Serum chemistry values and pH were normal.

On follow-up clinic visits in one month and three months the patient admitted to continuous alcohol ingestion, but denied any similar episodes. A glucose tolerance test was done and showed normal values except for a minimally elevated two hour value.

CASE 3. A 31-year-old man with a ten-year history of heavy alcohol abuse and idiopathic seizure disorder for which he took phenytoin, 300 mg per day, was brought in by his girl friend in a comatose state. He had stopped drinking alcohol approximately two days before. Since then, he had eaten and drunk little because of some anorexia, nausea and vomiting. His girl friend reported that he had a single grand mal seizure the previous night, but awoke and later retired to bed in a fully alert state. He had not taken any drugs or toxins, except for a marijuana cigarette three days before, and had discontinued taking his phenytoin at about the same time he stopped drinking. There was no personal or family history of diabetes, and the history was otherwise unremarkable.

On physical examination, the patient was tachypneic and tachycardiac with mild diaphoresis; findings included minimal facial flushing, slight hepatomegaly, and a stuporous state from which he was minimally arousable by maximal pain stimuli. A low blood glucose level was shown by Dextrostix, and he became fully alert and communicative after 100 grams of dextrose in 50 percent solution was infused intravenously. The blood glucose level was later found to be 27 mg per dl; other laboratory values are shown in Table 1. Treated with glucose and saline given intravenously, he was discharged in 12 hours, after serum chemistry values and arterial pH returned to normal, and he was eating regularly.

A follow-up clinic visit two months later showed that the patient had had no further similar

TABLE 1.—*Laboratory Summary of Nondiabetic Alcoholic Patients With Hypoglycemic Ketoacidotic Coma*

Case	*Arterial pH*	*Serum Acetest for Ketones*	*Urine Acetest for Ketones*	*Serum Glucose (mg/dl)*		*Serum Bicarbonate (mEq/liter) (normal 24-30)*		*Lactic Acid, Arterial (mEq per liter) (normal .5-1.5)*	*Serum β-hydroxybutyrate (mEq per liter) (normal<.05)*	*Anion Gap ($Na+K-[Cl+HCO_3]$)*	*Serum Bilirubin (mg/dl)*	*Serum Insulin (μU/ml)*	*SGOT (IU/liter) (normal<17)*	*SGPT (IU/liter) (normal<17)*	*Amylase (Caraway U) (normal<160)*
				Initial	*Discharge*	*Initial*	*Discharge*								
1	7.16	+	+	25	105	14	21	2.6	9.8	27	1.0	..	55	54	98
2	7.18	+	+	21	120	15	20	2.3	..	21	0.8	3	40	50	120
3	7.23	−	−	27	125	17	24	..	7.3	22	0.7	..	35	29	80
4	7.19	−	−	21	110	13	22	2.2	8.5	29	1.1	5	30	26	65
5	7.18	+	+	19	105	15	23	2.4	5.9	24	0.9	2	31	67	90
MEAN	7.19	..	..	23	..	15	..	2.4	7.9	25	0.9	3	38	45	91

episodes, but that he consumed alcohol regularly. A glucose tolerance test gave normal findings, as did liver function tests, except for a mildly elevated serum glutamic oxaloacetic transaminase value.

CASE 4. A 28-year-old man with a history of chronic alcoholism and alcohol withdrawal seizures was brought in by police after being found unresponsive in an alley, apparently having lain there for a number of hours. He later related that he had stopped drinking alcohol one or two days before, and that he had since been having epigastric pains with anorexia, nausea and vomiting. He had spent the night in the alley because of the warm weather, he claimed. He denied any toxin or drug ingestion, and said there was no personal or family history of diabetes. When he entered the emergency room, he was diaphoretic, with Kussmaul-type respirations and tachycardia.

On physicial examination the abdomen was normal and there was no hepatomegaly. The patient was comatose, barely responsive to painful physical stimuli. Dextrostix showed low serum glucose, and thiamine and 100 grams of dextrose were immediately given intravenously. He awoke quickly thereafter, alert and oriented. On laboratory studies, the blood glucose level was 21 mg per dl and the arterial pH was 7.19; other findings are shown in Table 1. A saline and dextrose solution was administered intravenously for 18 hours, at which time pH and electrolyte values had returned to normal. Because of persistent nausea, a prochlorperazine rectal suppository was administered, after which adequate oral intake of foods and liquids was restored.

On follow-up visit in six weeks it was found that the patient had continued drinking alcohol but had had no further similar episodes. An oral glucose tolerance test was done and results were within normal limits.

CASE 5. A 59-year-old man was brought by relatives to the emergency department one morning in a comatose state after he was found to be unresponsive at home. He had a 35-year history of heavy alcohol abuse, averaging half a pint of whiskey a day. He had stopped eating and drinking the previous morning, however, because of some epigastric pain with persistent nausea and vomiting. The patient later said there had been no toxin or drug exposure, nor any personal or family history of diabetes. The history was remarkable for an incompletely documented episode in 1973 when he presented to the emergency department in a comatose state with decorticate posturing. He was found at the time to be severely hypoglycemic, and regained consciousness upon the infusion of a concentrated dextrose solution. He was then admitted to hospital, where there was no recurrence of symptoms. A five-hour glucose tolerance test was carried out and showed no abnormalities. Percutaneous liver biopsy was also done and showed fatty changes.

On physical examination, the patient was diaphoretic, with a temperature of 35°C (95°F) rectally, tachycardia and rapid, labored breathing. He had moderate hepatomegaly, and responded only to deep painful stimuli with withdrawal motions. Dextrostix showed a low glucose level, so he was given thiamine intravenously, followed by 100 grams of glucose as a 50 percent solution. He awoke quickly thereafter, and was able to give a coherent history. Blood glucose level was reported to be 19 mg per dl and other laboratory findings (Table 1) showed metabolic acidosis with moderately reactive Acetest reaction in both serum and urine. Blood alcohol was undetectable, and the serum insulin value was low (2 μU per ml). He was admitted to hospital and treatment began with a continuous intravenous infusion of a glucose and saline solution, without bicarbonate. By late evening, body temperature, arterial pH and serum chemistry values were normal. The following day a five-hour glucose tolerance test was done and showed no abnormalities. The next morning an adrenocorticotropic hormone stimulation test was done and findings were normal. Later in the morning the patient asked to go home and was discharged in good condition. Follow-up in the medical clinic two months later indicated that no further similar episodes had occurred.

Results

All patients had a history of significant chronic alcohol intake, and generally were young, the average age being 40 years. The patients were all men, and all had a period of abstinence from alcohol for an average of two days immediately preceding their presentation in the hospital emergency department. This abstinence was usually related to the symptoms of anorexia, epigastric pain, nausea and vomiting. None of the patients had a personal or family history of diabetes, or

any renal, chronic lung or liver disease, nor was there any recent ingestion of drugs or toxins.

Each had gone to sleep the previous night, and was found to be in an unarousable state the next day upon presentation to the emergency department. The characteristics of the coma in each case were typical of hypoglycemic coma, with diaphoresis, tachypnea and tachycardia in all, and Kussmaul-type breathing noted in two patients. None of the patients was febrile, and one was hypothermic. Four of the five patients had evidence of hepatomegaly on physical examination. Bowel sounds were normal in all patients, without evidence of ileus. None appeared grossly hypovolemic on physical examination.

Admission laboratory data included low serum glucose values for every patient, verified by subsequent autoanalyzer values of less than 30 mg per dl in each case. Metabolic acidosis was present in every patient, with an average arterial pH of 7.19 and serum bicarbonate value of 14.8 mEq per liter. The average anion gap—serum Na + K − (serum Cl + serum HCO_3)—was 25 mEq per liter. Acetest examination of undiluted serum and urine was positive in three of the patients. In four of the five patients, including both patients with negative Acetest serum and urine reactions, serum β-hydroxybutyrate levels were notably elevated, with a mean value of 8.9 mEq per liter. Lactic acidosis did not appear to be present; arterial lactate was only mildly elevated in the four patients in whom it was measured. A toxicology screen of blood, urine and emesis specimens was done in each case and was negative in each. There was no evidence of hyperinsulinism, as serum insulin was appropriately low during hypoglycemia in each of the three patients in whom it was measured.

Despite the presence of abdominal pain, there was no evidence of pancreatitis in any of the patients: serum amylase was within normal limits in all patients. Serum bilirubin was normal in all five patients, although both serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase levels were somewhat elevated in all patients, averaging 38 and 45 units, respectively.

All patients were managed in a similar manner —first given a rapid bolus of a 50 percent dextrose solution, followed by prolonged intravenous infusion of approximately 3 liters of a saline and 5 percent dextrose solution over 12 to 18 hours while still in the emergency department. Coma in all cases responded rapidly to initial infusion of dextrose concentrates. Thereafter, the patients were observed closely and continued to do well with the glucose and saline infusions alone. Sodium bicarbonate was not used in any of the patients. One patient was given prochlorperazine because of nausea. At the time of discharge all patients had normal serum glucose levels and serum bicarbonate values were greater than 20 mEq per liter. They were all able to tolerate food and liquid without difficulty upon discharge. Each patient, along with any accompanying relative or friend, was told of the importance of continued and regular eating, and was instructed to return if difficulties with eating developed.

All patients did well after discharge with no recurrence of symptoms, although four of the patients admitted continued alcohol ingestion. A follow-up glucose tolerance test was carried out in each case and findings were normal.

Discussion

Although originally described in 1940 by Dillon,[3] only more recently has the entity of alcoholic ketoacidosis been further documented and investigated, primarily by Jenkins and associates[4] in 1971 and Levy and co-workers[5] in 1973. In the latter report, six episodes were described of metabolic acidosis in five nondiabetic, chronically alcoholic patients, each of whom had a history of protracted vomiting and abstention from food for several days. One of the patients presented in an unconscious state, and all were found to be significantly acidotic, with an average arterial pH of 7.16, ranging from 6.96 to 7.29, with anion gaps of 15 to 34 mEq per liter. Two patients died, one with aspiration pneumonia and the other with cardiac arrest. Only this latter patient was found to be hypoglycemic; all others were noted to have normal or elevated serum glucose levels. Similarly, in the reported cases of alcoholic ketoacidosis described by Jenkins and co-workers,[4] Cooperman and associates[6] and Fulop and associates,[12] all but two patients were noted to have normal or elevated serum glucose levels. In contrast, our patients with alcoholic ketoacidosis presented in profound hypoglycemic coma, responsive in each case to concentrated glucose solutions given intravenously.

Heretofore, a striking preponderance in the literature of women with alcoholic ketoacidosis—15 of 19 cases—has been noted by Cooperman,[6]

although this was not true in the cases reported by Fulop and co-workers.[12] On the other hand, the combination of alcoholic hypoglycemic coma and ketoacidosis seems to occur most often in men. The patients were similar, however, in other respects—most of them having had a heavy alcohol intake up until one to three days before presentation, at which time drinking and food consumption were stopped, usually because of nausea, vomiting and epigastric distress. There was no history of toxin or drug ingestion, nor was there any evidence of diabetes mellitus found on later glucose tolerance testing. Each of the patients went to sleep the previous night and was found to be unarousable the next day upon presentation to the emergency department. Finally, hypothermia, which was a common feature in Harvey's series,[1] was present in only one of our five patients.

Both the metabolic acidosis and hypoglycemia in each of our patients were corrected within 12 to 18 hours with intravenous administration of glucose and saline, as has been reported by others in the literature.[4-6,11] Thiamine was given intravenously before glucose infusion in most cases in order to prevent possible precipitation of Wernicke disease. Recovery was complete without the introduction of alkali. Antiemetics were used in one case for symptomatic relief of nausea, so that oral intake could be reestablished. Four of the five patients were managed as outpatients in the emergency department and were discharged directly from there, rather than being admitted to hospital. One of the patients, who was also hypothermic, was admitted to hospital, but his body temperature, pH and serum chemistry values had returned to normal within 12 hours. At the time of clinic follow-up, none of the patients reported any continued difficulties, though a number had later recommenced their alcohol intake.

It is of note that in two of our patients Acetest reactions were not positive for ketones in either serum or urine, despite clear-cut acidosis in both of them. Serum lactic acid was measured in one of these two patients and was normal. The most likely explanation for this observation is the relative insensitivity of the nitroprusside reagent to acetone and especially β-hydroxybutyrate.[13] In fact, β-hydroxybutyrate levels were substantially elevated in both of these patients, and indeed in all four patients in whom this measurement was made. As has been shown by Levy and colleagues[5] and Cooperman and associates,[6] ketone bodies in alcoholic ketoacidosis are mainly in the form of β-hydroxybutyrate, with relatively low levels of acetoacetate, probably because of the high NADH/NAD ratio (nicotinamide adenine dinucleotide [reduced form]/nicotinamide adenine dinucleotide). Hence, the Acetest reaction may show little or no reactivity despite the presence of ketoacids, as in our series and others.[5,6,12] If this is not kept in mind, it can lead to underestimation of the degree of ketosis or failure to recognize it.

The precise mechanism and cause of the alcoholic hypoglycemia, as well as the ketoacidosis, remain uncertain. It is also unknown why some patients become hyperglycemic and ketoacidotic. Cooperman[6] suggested that hormonal—ovarian and placental—mechanisms might be playing a role, since most of the reported cases of alcoholic ketoacidosis occurred in women. This appears unlikely, however, in that both Fulop's series[12] and our own show a predominance of men. The factors contributing to the hypoglycemia are probably numerous. First, patients have typically not eaten for a number of hours to days, depleting available hepatic glycogen stores. Second, hepatic gluconeogenesis has been suppressed by prior ethanol intake. This suppression of gluconeogenesis, in turn, is thought to result from the pronounced increase in the NADH/NAD ratio generated during ethanol metabolism. This elevated level of NADH can persist for an abnormally long period in the livers of alcoholics.[14] Finally, it has been suggested that decreased levels of circulating alanine may account for the diminished gluconeogenesis in the presence of ethanol.[15,16]

While fasting, the precursors of hepatic gluconeogenesis include amino acids, lactate and glycerol. Amino acids enter this pathway by conversion either to pyruvate or, via the tricarboxylic acid cycle, to oxaloacetate, and thence to phosphoenolpyruvate. A high NADH/NAD ratio, however, is an effective suppressant of the tricarboxylic acid cycle. Lactate, which has been noted to be slightly elevated in some patients—and in two of the four patients in our series in whom it was measured—must be oxidized to pyruvate in order to enter the gluconeogenic pathway. This oxidation is inhibited by the high NADH/NAD ratio, however, and the reduction of pyruvate to lactate is favored, with potentially significant accumulation of the latter.

The mechanism of the coexisting ketoacidosis in our patients is perhaps equally obscure. During the prolonged fasting there is increased fat mobi-

lization peripherally, with a resultant increased fat load upon the liver. In very large amounts, alcohol can itself produce peripheral fat mobilization. Cortisol and growth hormone levels have been found to be elevated in patients with alcoholic ketoacidosis by Levy and co-workers,[5] and may represent another important factor in the increased lipolytic rate. In the liver, oxidation of these increased amounts of free fatty acids is carried out by the NAD-requiring Krebs cycle. As discussed above, this is impeded because of the altered redox state from ethanol metabolism, resulting in the production of ketones and ketoacidosis. Substantial ultrastructural changes have been noted in the hepatic mitochondria of alcoholics,[17] and it may be that hepatic ketone production is further enhanced by favoring the rate of fatty acyl entry into the mitochondria, controlled by the enzyme, fatty acyl carnitine transferase,[18] and by loosening of hepatic mitochondrial respiratory control, as suggested by Cooperman.[6] The defect and ketosis are rapidly reversed by the intravenous infusion of glucose.

The fact that five cases of hypoglycemic coma with ketoacidosis were observed in nondiabetic alcoholic patients in the course of two months in a large city emergency room, suggests that this syndrome is probably not uncommon among the chronic alcoholics seen in emergency departments of large hospitals. During this time, three additional alcoholic patients with a similar history of recent food and alcohol abstinence were seen in the emergency department with complaints of mild abdominal pain, nausea and vomiting, and were found to be in nondiabetic ketoacidosis, but were normoglycemic. To give some perspective, 15 cases of diabetic ketoacidosis were seen in the emergency department by the same observers during this same period. Perhaps less severe degrees of this metabolic imbalance masquerade as acute alcohol intoxication, and may be unrecognized in busy emergency departments, particularly when a patient is asleep on a stretcher for several hours during which an intravenous dextrose solution with the usual vitamin supplements is being given—which is routine. This group of patients undoubtedly will recover. However, yet another, less fortunate group of patients who also may have simply appeared to be intoxicated may be sent home without intravenously given glucose or even a meal. Therefore, particularly because of the easily reversible nature of hypoglycemia and alcoholic ketoacidosis, and because of their potentially serious outcome if left untreated, these entities must enter prominently in the differential diagnosis of alcoholic patients with altered mental status.

REFERENCES

1. Brown TM, Harvey AM: Spontaneous hypoglycemia in "smoke" drinkers. JAMA 117:12-15, 1941
2. Freinkel N, Singer DL, Arky RA, et al: Alcohol hypoglycemia—I. Carbohydrate metabolism of patients with clinical alcohol hypoglycemia and the experimental reproduction of the syndrome with pure ethanol. J Clin Invest 42:1112-1131, 1963
3. Dillon ES, Dyer WW, Smelo LS: Ketone acidosis of nondiabetic adults. Med Clin North Am 24:1813-1822, 1940
4. Jenkins DW, Ecel RE, Craig JW: Alcoholic ketoacidosis. JAMA 217:177-183, 1971
5. Levy LJ, Duga J, Girgis M, et al: Ketoacidosis associated with alcoholism in nondiabetic subjects. Ann Intern Med 78:213-219, 1973
6. Cooperman MT, Davidoff F, Spark R, et al: Clinical studies of alcoholic ketoacidosis. Diabetes 23:433-439, 1974
7. Miller PD, Heinig RE, Waterhouse C: Treatment of alcoholic acidosis. Arch Intern Med 138:67-72, 1978
8. Marbach EP, Weil MH: Rapid enzymatic measurement of blood lactate and pyruvate. Clin Chem 13:314-325, 1967
9. Larky H: Practical Clinical Biochemistry. London, W Heinemann Medical Books Ltd, 1967, p 618
10. Antonis A, Clark M, Pilkington T: A semiautomated fluorometric method for the enzymatic determination of pyruvate, lactate, acetoacetate, and beta-hydroxybutyrate levels in plasma. J Lab Clin Med 68:340-356, 1966
11. Morgan CR, Lazaron A: Immunoassay of insulin using a two-antibody system. Proc Soc Exp Biol Med 110:29-32, 1962
12. Fulop M, Hoberman HD: Alcoholic ketosis. Diabetes 24: 785-790, 1975
13. Lee CT, Duncan GG: Diabetic coma: The value of a simple test for acetone in plasma—An aid to diagnosis and treatment. Metabolism 5:144-149, 1956
14. Leevy CM: Clinical diagnosis, evaluation and treatment of liver disease in alcoholics. Fed Proc 26:1474-1481, 1968
15. Siegal FL, Roach MK, Pomeroy LR: Plasma amino acid patterns in alcoholism: The effects of ethanol loading. Proc Natl Acad Sci 51:605-611, 1964
16. Kreisberg RA, Siegal AM, Owen WC: Ethanol-induced hyperlactatemia: Inhibition of lactate utilization. J Clin Invest 50:166-174, 1971
17. Lefevre A, Adler H, Lieber CS: Effect of ethanol on ketone metabolism. J Clin Invest 49:1775-1782, 1970
18. McGarry JD, Meier JM, Foster DW: The effects of starvation and refeeding on carbohydrate and lipid metabolism *in vivo* and in the perfused rat liver—The relationship between fatty acid oxidation and esterification in the regulation of ketogenesis. J Biol Chem 248:270-278, 1973

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Mannitol

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Mannitol may be useful clinically both as a diuretic and as an obligate extracellular solute. As a diuretic it can be used to treat patients with intractable edema states, to increase urine flow and flush out debris from the renal tubules in patients with acute tubular necrosis, and to increase toxin excretion in patients with barbiturate, salicylate or bromide intoxication. As an obligate extracellular solute it may be useful to ameliorate symptoms of the dialysis disequilibrium syndrome, to decrease cerebral edema following trauma or cerebrovascular accident, and to prevent cell swelling related to renal ischemia following cross-clamping of the aorta. Largely unexplored uses for mannitol include its use as an osmotic agent in place of dextrose in peritoneal dialysis solutions, its use to maintain urine output in patients newly begun on hemodialysis, and its use to limit infarct size following acute myocardial infarction.

MANNITOL IS A 6-carbon alcohol with a molecular weight of 182, prepared commercially by the reduction of dextrose. Although it has an important place in current therapy, few physicians fully understand its chemistry, mode of action or clinical applicability. Since 1940, when Smith and associates[1] showed that mannitol clearance closely reflected glomerular filtration rate in man, there has been clinical interest in mannitol. However, recent emphasis on the role of cell swelling in the genesis of ischemic tissue damage has rekindled awareness of the medical uses of mannitol as more than only an osmotic diuretic.

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Pharmacokinetics

Because orally administered mannitol is not absorbed, it must be administered parenterally. It distributes almost entirely in the extracellular fluid, very little penetrating cells. As a result, it is virtually inert, only 7 percent to 10 percent being metabolized, probably in the liver, while the rest is freely filtered by the glomeruli and excreted intact in the urine. About 7 percent is reabsorbed by the renal tubules. With normal kidney function, after a single intravenous dose, the half-life of mannitol in the circulating plasma is 15 minutes.[2] Of an injected dose, 90 percent is recovered in the urine after 24 hours.[3] However, with severe renal insufficiency the rate of mannitol excretion is greatly reduced and retained mannitol may increase extracellular tonicity leading to a shift of water out of cells, expanding the extracellular

fluid as well as inducing an apparent hyponatremia with increased serum osmolality such as occurs in hyperglycemia. Therefore, mannitol should be used cautiously under these conditions.

Physiological Effects

Renal

Osmotic diuretics are obligate solutes of low molecular weight, which are freely filtered at the glomerulus and poorly reabsorbed by the renal tubules. The resulting high urinary concentration profoundly affects renal water and sodium reabsorption. An almost ideal prototype, mannitol was used extensively in early physiological studies of osmotic diuresis. Wesson and Anslow[4] concluded that the proximal tubule was the primary site of action of mannitol's osmotic diuretic effect. More recently, however, Seely and Dirks[5] have precisely defined this phenomenon, their work being confirmed later by others.[6] Using micropuncture techniques, they elegantly demonstrated that half the effect of mannitol occurs proximally and half occurs in the ascending limb of the loop of Henle and proposed the following mechanism: The osmotic effect of mannitol depresses proximal reabsorption of water more than sodium, thereby decreasing proximal tubular fluid sodium concentration. Consequently, the gradient for passive sodium reabsorption in the thin ascending limb of the Henle loop is decreased. The natriuresis of mannitol diuresis, therefore, results largely from decreased sodium reabsorption in the loop of Henle. In addition, changes in medullary tonicity secondary to a mannitol augmentation of medullary blood flow may also effect sodium excretion.[7] As sodium delivery to distal tubular exchange sites increases, potassium excretion may rise during mannitol diuresis.

The effect of mannitol on renal hemodynamics may be both direct and indirect. Ternes and coworkers[8] showed that there was a dose dependent increase in renal vascular resistance in isolated perfused dog renal artery strips exposed to varying perfusate concentrations of mannitol. In contrast, others[9-11] found there to be an increase in total renal blood flow *in vivo* in animals, independent of the plasma volume increase. No comparable data for humans are available.

Lilien[12] reported a biphasic dose related response in rats, which might provide a unified view of the mannitol effect on renal hemodynamics. At lower doses, there is definite vasodilatation probably mediated through efferent arteriolar dilatation, which could also contribute to the slight decrease in glomerular filtration rate during mannitol infusions. Conversely, at higher doses, the vasoconstrictor effect reported by Ternes and associates[8] supervenes.

Glomerular filtration rate falls slightly in animals and humans given mannitol. When mannitol is present in the proximal nephron and prevents, through its osmotic effect, sodium and water reabsorption, filtrate volume and pressure in this nephron segment rise. It is this increased intratubular pressure after mannitol administration that decreases glomerular filtration rate by Starling's law. Efferent arteriolar dilatation after mannitol is administered may occur (as has been mentioned) and may also play a role in the decreased glomerular filtration rate.

When proximal tubular sodium reabsorption is inhibited for any reason, calcium excretion in the urine increases. The precise mechanism of this coupling of sodium and calcium excretion is unknown. Even though, as explained above, decreased proximal tubular sodium reabsorption does not account for the bulk of the natriuresis after mannitol administration, the amount of sodium escaping proximal tubular reabsorption is increased. As a result, calcium excretion increases proportionately.[13,14] Independent of the natriuresis, urinary phosphate excretion also increases during mannitol diuresis.[15]

The only renal histologic effect of mannitol infusions in animals[16] or humans[17] is the same reversible proximal tubular cell vacuolization reported after sucrose and other osmotic diuretics. However, it is not associated with any functional tubular defects.

Cardiovascular

Intravenously injected mannitol is confined to the extracellular fluid space. The increased tonicity obligates water to move from the intracellular to the extracellular fluid to maintain osmotic equilibrium. With each 182 mg per dl increase in mannitol concentration, a 10 milliosmole increase in extracellular fluid osmolality occurs with the same proportionate dilution of all serum electrolytes as occurs in hyperglycemia. Various amounts of plasma volume expansion have been reported with mannitol infusion ranging from 1 ml per kg of body weight per 5 grams of mannitol infused[18] to 3 ml per kg of body weight per 5 grams of

mannitol infused,[19] depending on body osmolarity and the relationship among plasma volume, extracellular fluid and total body water in the individual animal or person. With each 100 mg per dl increase in mannitol concentration in the extracellular fluid, serum sodium falls 1.6 to 2.6 mEq per liter.

After the expansion of the extracellular fluid and blood volume by injection of mannitol mean arterial pressure,[20,21] cardiac output,[20,21] heart rate,[21,22] coronary blood flow[20] and left ventricular end diastolic pressure[22] all increase. In isolated perfused artery segments, physiologic doses of mannitol cause vasodilatation and block the vasoconstrictor effects of norepinephrine.[23]

Cerebrovascular Disease

Mannitol has several physiologic effects on the cerebrovascular system. Increased cerebral blood flow,[24] increased cerebral oxygen consumption[24] and decreased cerebrospinal fluid pressure[24,25] have all been documented. The decreased cerebrospinal fluid pressure, in spite of increased cerebral blood flow, is of interest. Since mannitol cannot cross the blood brain barrier, it causes water to move out of the brain into the extracellular fluid. This decrease in brain water is the cause of the fall in cerebrospinal fluid pressure. The movement of water out of the brain in response to the osmotic effect of mannitol decompresses the brain when cerebral edema is present. It is more effective than urea in this regard since urea slowly crosses the blood brain barrier and therefore maintains a lower osmotic gradient for water movement out of the brain.

Ocular System

Mannitol profoundly lowers intraocular pressure when given intravenously[26,27] just as it lowers cerebrospinal fluid pressure. In addition, when applied topically to the cornea mannitol may be absorbed and also have an ocular hypotensive effect.[28]

Concept and Importance of Cell Swelling

In a variety of organs, including kidney, heart and brain, following relatively brief periods of vascular occlusion, reperfusion fails to restore normal circulation.[29,30] This phenomenon of impaired reflow is caused by vascular endothelial cell swelling induced by the ischemic anoxia. Normally, the diffusion of sodium into and of potassium out of cells down existing concentration gradients is opposed by a *pump* requiring energy from oxidative metabolism, which constantly moves sodium out of cells and potassium into cells against the concentration gradients. During hypoxia the metabolic energy required by this pump which normally extrudes sodium from cells is lacking. As a result, sodium accumulates intracellularly. To maintain osmotic equilibrium, water shifts in, swelling the endothelial cell, impairing the flow of blood. Following prolonged depression of blood flow, tissue death results. However, if flow can be restored in time, reversal of the ischemic injury can occur. Restoration of flow, which is dependent upon the removal of intracellular water with consequent shrinking of endothelial cells to normal size, can be readily accomplished by the intravenous administration of hypertonic mannitol solutions to increase extracellular fluid osmolality.

Clinical Uses

Diuretic

Being an obligatory solute, mannitol may be used either as an osmotic diuretic per se to maintain water excretion or potentiate the action of saluretic diuretics (see below). In the clinical edemas of severe nephrotic syndrome,[31] cirrhosis with ascites[32] or congestive heart failure, conventional diuretics, for example, the loop diuretics, may not promote much diuresis partly because of greatly increased proximal tubular reabsorption of sodium and water caused by ineffectively circulating volume. Under these circumstances, mannitol, by reducing proximal tubular reabsorption of sodium and water, increases the sodium load reaching the more distal tubular segments, enhancing the effect of the saluretics. Because enhanced distal nephron sodium reabsorption may quantitatively play a greater role in sodium retention in these conditions, however, the use of mannitol alone might not be sufficient to produce the desired diuresis.

Clinically, mannitol has also been used to treat severe water overload and hyponatremia. In these situations, the hyponatremia is dilutional. The osmotic effect of mannitol in the urine, as discussed earlier, causes a diuresis with an excess of water over electrolytes being excreted. By administering 25 gram boluses of hypertonic mannitol intravenously hourly, as needed to maintain urine flow, water excretion can be notably augmented. Each 5 grams of mannitol ultimately

leads to excretion of approximately 100 ml of water in excess of electrolyte, and serum sodium will rise. Thus, massive water diuresis with rapid correction of the hyponatremia follows intravenous infusion of hypertonic mannitol. However, in patients with existing intravascular volume overload or with severe myocardial disease, such infusions may excessively expand intravascular volume producing pulmonary congestion or frank pulmonary edema.

Prevention of Acute Renal Failure

Although some have questioned whether mannitol administration may prevent the development of ischemic acute renal failure (ARF),[33,34] considerable experimental and clinical data support this prophylactic application.[35-46] The reduction in ischemic injury to the kidneys of rats and dogs by prophylactic or early mannitol infusions is well documented.[35-40] For example, in rats mannitol infused at the time of initiation of ischemia not only increased renal blood flow[36] but also significantly decreased cell swelling and the resultant rise in blood urea nitrogen and creatinine.[35] However, in dogs, the renal failure following hemorrhagic hypotension has been reported to be unaffected by mannitol in one study,[37] whereas others have shown there to be significant increases in creatinine and para-aminohippurate clearances (glomerular filtration rate and renal blood flow) when mannitol was given before hypotension was induced.[38-40]

The benefit of mannitol in human ischemic renal disease is suggestive, if not conclusive. In 37 patients in whom oliguria developed in the absence of intravascular volume depletion, Luke and co-workers[41] infused 100 ml of a 20 percent mannitol solution intravenously over 10 to 30 minutes and measured urine output. If the output reached 50 ml per hour over the next two hours, no further mannitol was given. If the output increased, but less than 50 ml per hour, the same dose was repeated. By this technique, responders and nonresponders to mannitol could be identified. The responders subsequently had oliguria for less than 50 hours and urine-to-plasma osmolality ratios greater than 1.05, and renal failure did not occur. This strongly suggested that the mannitol infusion either identified the nonresponders as patients who would progress to renal failure or was able to reverse the developing renal failure in the responders as reported by Eliahou.[47] Similarly, in a variety of toxin or pigment induced renal failure in animals,[42,43] mannitol, if given early, has been shown to ameliorate or to prevent renal failure. Finally, Dawson[45,46] has reported extensive experimental and clinical evidence that the severe acute tubular necrosis (ATN) which may complicate the postoperative course of hyperbilirubinemic patients may be prevented by establishing and maintaining mannitol diuresis until serum bilirubin concentration has fallen to an acceptable level.

In summary, the evidence in animals and humans is highly suggestive that mannitol, either by decreasing glomerular capillary endothelial cell swelling and thus restoring glomerular blood flow; decreasing proximal tubular cell swelling and promoting movement of intratubular debris[48] that could be causing tubular obstruction; diluting urine and washing out toxin; or improving renal perfusion, can ameliorate or prevent development of acute renal failure from a variety of causes. In oliguric patients with repleted intravascular volume we recommend the following mannitol trial:

- Rapidly inject 12.5 to 25 grams of 20 percent to 25 percent solution of mannitol intravenously and measure urine volume and specific gravity hourly.
- If urine output in the next hour is less than 50 ml repeat the same dose.
- If still no response, established acute renal failure is present and no more mannitol should be given.
- If the patient responds, either incipient acute renal failure has been reversed or oliguric acute renal failure has been converted to nonoliguric, either of which has a better prognosis than oliguric acute renal failure. Underlying pathogenetic factors— for example, extracellular fluid depletion— should be corrected.
- Be aware of possible complications of mannitol therapy (see below).

Dialysis

Dialysis disequilibrium is a common complication of rapid, efficient hemodialysis. Manifestations of this syndrome include nausea, vomiting, headache, blurred vision and seizures all caused by brain swelling and increased intracranial pressure. Dialysis induced hypotension (in the absence of volume depletion) and muscle cramps are also felt by many[49,50] to be part of this syndrome.

Most symptoms result from brain and muscle cell swelling due to water shifts following rapid removal of solute from the intravascular space with resultant disruption of the normal intracellular-extracellular fluid osmotic equilibrium. The relation of dialysis induced hypotension to osmolality changes remains to be defined. Hagstam and coworkers[49] and Rodrigo and associates[50] showed that many features of this syndrome can be prevented by infusing hypertonic mannitol into the venous return line of the dialyzer continuously during dialysis. In functionally anephric patients, however, mannitol should be used for only the first few dialyses or intermittently when severe symptoms related to disequilibrium occur[50] to avoid mannitol accumulation in the extracellular fluid.

Mannitol has two other possible uses in dialysis. First, it may be added to peritoneal dialysate to increase the osmolality, thus promoting fluid removal, particularly in diabetic patients who become severely hyperglycemic after continued use of conventional hypertonic glucose peritoneal dialysate. Second, mannitol infusions might be given to maintain osmotic load and urine output after dialysis preventing virtual anuria in patients undergoing hemodialysis or peritoneal dialysis therapy. Maintaining some urine flow would aid in fluid management and promote some potassium excretion in these patients. The later use for hypertonic mannitol has not been adequately tested, however.

Renal Transplantation

Mannitol may be administered safely to patients with renal transplants to distinguish post-transplant acute tubular necrosis and acute rejection. Anderson and associates[51] carried out studies in five renal transplant patients with previous bilateral nephrectomies, who were oliguric following transplantation. Acute rejection eventually was found in four of the five in whom diuresis occurred after injections of mannitol and ethacrynic acid.

Diagnostic Tool

Mannitol has been used to diagnose renal disease unrelated to acute renal failure. Mannitol pyelography may be used to visualize renal collecting structures not seen on routine intravenous pyelogram because of high blood urea nitrogen,[52] as well as to magnify the intravenous pyelogram abnormalities associated with unilateral renal artery stenosis.[50] Similarly, partial versus complete and central versus renal diabetes insipidus[54] may be distinguished by comparing the change in free-water clearance (CH_2O) in response to infusion of hypertonic mannitol alone (which stimulates antidiuretic hormone release and decreases free water clearance) in contrast to infusion of mannitol plus antidiuretic hormone to see if the response to mannitol can be augmented. The details are nicely outlined by Oetliker and associates.[54]

Toxin Excretion

Mannitol infusion has been used extensively in prophylatic and active treatment of intoxications with endogenous and exogenous substances whose clearance is increased by mannitol.[55] Rapid excretion of secobarbital,[55] eucalyptus oil,[56] salicylates[57] and bromides[58] has been reported after mannitol administration. In addition, endogenous substances such as uric acid,[59,60] hemoglobin and myoglobin are rapidly excreted without renal damage after mannitol administration. Mannitol may also modify or prevent the nephrotoxicity of certain chemotherapeutic agents. This has been clearly shown for cis-platinumdisamminedichloride[61,62] and is suggestive for tetracyline[63] and amphotericin B.[64-66]

Cerebrovascular Disease

Because cerebral edema or intracranial pressure is reduced following rapid infusion of 20 percent mannitol solution, this technique has been widely used in treating cerebrovascular diseases including postangiography brain swelling,[67] Reye syndrome,[68] hypoglycemia,[69] trauma[70,71] and the cerebral edema following neurosurgery,[72,73] as well as dialysis disequilibrium. A 20 percent to 50 percent reduction in intracranial pressure 30 to 45 minutes after mannitol administration has been noted. This effect may last up to several hours. A small rebound in pressure is then noted,[74] but this is much less than that seen after urea administration. An analagous effect of mannitol on spinal cord pressure after trauma in cats has been noted,[75] suggesting that mannitol may be used to decrease spinal cord swelling after trauma, surgical operation or irradiation. Whether mannitol can promote resorption of chronic subdural hematomas has been disputed[76,77] and at present is unsettled. Finally, there is a suggestion that

mannitol can alter the blood brain barrier and increase the entry of intravenously administered antibiotics into the central nervous system.[78]

Cardiovascular Disease

Oliguria with decreased glomerular filtration rate and renal plasma flow commonly occurs following open heart surgical procedures under cardiopulmonary bypass. The mechanisms are not fully understood but may reflect a degree of acute renal failure. Mannitol given either intravenously or as a prime for the bypass pump, may decrease the magnitude and severity of these changes.[79,80] In patients in whom aortic operations are done with cross-clamping of the aorta below the renal arteries, analogous changes develop in renal function, which are also prevented by intravenous mannitol given just before cross-clamping.[81] Finally, more recently the protective effect of mannitol on ischemic myocardium has been intensively studied. When given to animals just before experimental coronary artery occlusion, mannitol decreases cell swelling, water content and necrosis in anoxic myocardial cells.[82-90] It increases total and collateral myocardial blood flow, reduces electrocardiographic evidence of ischemia, decreases coronary vascular resistance and increases cardiac output. However, such administration of mannitol after coronary occlusion has not limited infarct size, and the role of mannitol therapy in human coronary artery disease remains to be elucidated.

Miscellaneous Uses

Mannitol has been used to decrease pulmonary vascular resistance and increase alveolar ventilation in the acute respiratory distress syndrome,[91] to terminate pregnancies,[92] to stop hematuria as-

TABLE 1.—*Clinical Applications of Intravenously Given Mannitol Solutions*

I. Diagnostic Evaluation of Acutely Oliguric Patient
   A. Test dose of 12.5 to 25 grams mannitol (20 percent to 25 percent solution) should be given in intravenous push over three to five minutes.
   B. If no response (>50 ml urine/hour) repeat the same dose in one hour.
   C. If still no response, no further mannitol should be given and treatment for acute tubular necrosis instituted.

II. Therapeutic Uses
   A. Prevention of acute renal failure (such as after cardiovascular surgical operation)
      1. Test dose as above followed by a priming dose of sufficient concentrated (20 percent) mannitol over an hour to bring the priming dose to 50 grams.
      2. Maintain urine output at 50 ml/hour with intravenous infusion of 5 percent mannitol plus 20 mEq sodium chloride/liter and 1 gram calcium gluconate/liter. Later, if needed, appropriate concentrations of potassium acetate, magnesium sulfate and more sodium chloride should be given as indicated.
   B. Treatment of Oliguria
      1. Test dose as above.
      2. If response is noted, look for underlying cause of oliguria other than acute tubular necrosis, for example, hypovolemia due to subtle cause of extracellular fluid contraction, such as third spacing.
   C. Adjunctive Therapy for Intoxications
      1. Test dose as above followed by priming dose (IIA).
      2. Maintain urine output at 150 to 500 ml/hour with a continuous intravenous infusion of 5 percent mannitol, each liter containing 45 mEq sodium chloride, 24 mEq sodium acetate, 1 gram calcium gluconate, 1 gram magnesium sulfate and 20 mEq potassium acetate. If alkalinization of the extracellular fluid and urine is desired as in treatment of barbiturate intoxication less sodium chloride and more sodium acetate may be given depending on hourly checks of urine pH or blood gases. Serum electrolytes and osmolarity should be monitored periodically.
   D. Treatment of Elevated Intracranial or Intraocular Pressure
      1. 100 to 150 grams (15 percent or 20 percent solution) given over 30 to 60 minutes. Repeat as necessary to control intracranial or intraocular pressure.
      2. Use 60 to 90 minutes before craniotomy or ocular surgery for maximal effect.
   E. Treatment of Water Intoxication With Symptomatic Dilutional Hyponatremia
      1. Test dose followed by a priming dose as above (IIA).
      2. Give 20 percent mannitol as 25 gram boluses hourly or by continuous infusion at a rate of 100 to 125 ml per hour.
   F. Potentiation of Diuresis in Patients With Intractable Cardiac, Cirrhotic and Nephrotic Edema
      1. Give intravenous injection of near maximal dose of ethacrynic acid or furosemide.
      2. Follow immediately with test dose of mannitol as described above followed by slow intravenous infusion of 10 percent to 20 percent mannitol at a rate of 50 to 75 ml/hour.
      3. Patient's cardiovascular status including central venous pressure, urine output and osmolarity and serum electrolytes should be carefully monitored during the infusion.

sociated with sickle cell trait[93] and to augment iodine 131 uptake in the treatment of thyroid cancer.[94]

Administration

Specific recommendations for intravenous administration of mannitol are presented in Table 1 for each of several clinical applications.

Precautions

One case report of an allergic reaction associated with mannitol administration has been published.[95] However, the relationship is unclear since mannitol is inert and no other cases have been reported. On the other hand, in a patient with poor renal function and incipient heart failure, excessive volume expansion following mannitol infusion can be a serious side effect and mannitol should be administered very cautiously in such a situation. After hypertonic mannitol administration, particularly of bolus doses,[96] dilutional hyponatremia and cellular dehydration may result from the movement of water out of cells in response to increased extracellular fluid tonicity. In a patient with good renal function this abnormality is of little consequence and is rapidly corrected as mannitol is excreted. In a patient with poor kidney function, however, sustained hyperosmolality, hyponatremia and cellular dehydration may be serious complications.[97] Rarely, hypernatremia and dehydration from excessive water loss in response to larger rapid infusions of hypertonic mannitol in patients with functioning kidneys, and occasionally mild hyperkalemia of unclear origin,[98] may occur. Finally, in uremic dogs given mannitol pronounced decreases in cerebrospinal fluid pH resulting in death have been noted.[99] Similar changes in cerebrospinal fluid pH in human beings with uremia after mannitol administration have not been studied.

REFERENCES

1. Smith WW, Finkelstein N, Smith HW: Renal excretion of hexitols and their derivatives and of endogenous creatinine-like chromogen in dog and man. J Biol Chem 135:231-250, 1940

2. Oldendorf WH, Kitano M: The early disappearance of extracellular tracers from plasma after I.V. injection. Soc Exp Biol Med 141:940-943, 1972

3. Dominguez R, Corcoran AC, Page IH: Mannitol—Kinetics of distribution, excretion and utilization in human beings. J Lab Clin Med 32:1192-1202, 1947

4. Wesson LG, Anslow P: Excretion of sodium and water during osmotic diuresis in dogs. Am J Physiol 153:465-474, 1948

5. Seely JF, Dirks JH: Micropuncture study of hypertonic mannitol diuresis in the proximal and distal tubule of the dog kidney. J Clin Invest 48:2330-2340, 1969

6. Gennari FJ, Kassirer JP: Osmotic diuresis. N Engl J Med 291:714-720, 1974

7. Lilien OM, Jones SG, Mueller CB: The mechanism of mannitol diuresis. Surg Gynecol Obstet 117:221-228 1963

8. Ternes SP, Lilien OM, Chamberlain W: A direct vasoconstrictor effect of mannitol on the renal artery. Surg Gynecol Obstet 141:223-226, 1975

9. B'alint P Szoocs E, Tarj'an E, et al: Autoregulation of renal circulation in mannitol-loaded dogs. Int Urol Nephrol 7:65-78, 1975

10. Velasquez MT, Notargiacomo AV, Cohn JN: Comparative effects of saline and mannitol on renal cortical blood flow and volume in the dog. Am J Physiol 224:322-327, 1973

11. Detmer DE, Zimmerman JM, King TC: Mannitol diuresis: The relationship of plasma volume to renal blood flow. J Surg Res 5:552-555, 1965

12. Lilien CM: The paradoxical reaction of renal vasculature to mannitol. Invest Urol 10:346-353, 1973

13. Parfitt AM: The acute effects of mersalyl, chlorothiazide and mannitol on the renal excretion of calcium and other ions in man. Clin Sci 36:267-282, 1969

14. Sotorn'ik I, Schuck O, Stribrna J: Influence of diuretics on renal calcium excretion. Experientia 25:591-592, 1969

15. Maesaka JK, Berger ML, Bornia ME, et al: Effect of mannitol on phosphate transport in intact and acutely thyroparathyroidectomized rats. J Lab Clin Med 87:680-691, 1976

16. DiScala VA, Mautner W, Cohen JA, et al: Tubular alterations produced by osmotic diuresis with mannitol. Ann Intern Med 63:767-775, 1965

17. Janssen CW Jr: Osmotic nephrosis—A clinical and experimental investigation. Acta Chir Scand 134:481-487, 1968

18. Barry KG, Berman AR: Mannitol infusion—III. The acute effect of the intravenous infusion of mannitol on blood and plasma volumes. N Engl J Med 264:1085-1088, 1961

19. Hoff JE, Deavers S, Huggins RA: Effect of hypertonic glucose and mannitol on plasma volume. Proc Soc Exp Biol Med 122:630-634, 1966

20. Willerson JT, Curry GC, Atkins JM, et al: Influence of hypertonic mannitol on ventricular performance and coronary blood flow in patients. Circulation 51:1095-1100 1975

21. Atkins JM, Wildenthal K, Horwitz LD: Cardiovascular responses to hyperosmotic mannitol in anesthetized and conscious dogs. Am J Physiol 225:132-137, 1973

22. Raizner AE, Costin JC, Croke RP, et al: Reflex, systemic and local hemodynamic alterations with experimental hyperosmolality. Am J Physiol 224:1327-1333, 1973

23. Krishnamurty VS, Adams HR, Smitherman TC, et al: Influence of mannitol on contractile responses of isolated perfused arteries. Am J Physiol 232:H59-H66, 1977

24. Goluboff B, Shenkin HA, Haft H: The effects of mannitol and urea on cerebral hemodynamics and cerebrospinal fluid pressure. Neurology 14:891-898, 1964

25. Cottrell JE, Robustelli A, Post K, et al: Furosemide an mannitol induced changes in intracranial pressure and serum osmolality and electrolytes. Anesthesiology 47:28-30, 1977

26. Adams RE, Kirschner RJ, Leopold IH: Ocular hypotensive effect of intravenous mannitol. Arch Ophth 69:55-58, 1963

27. Zayed A, Fouad AR: The role of mannitol osmotherapy in retinal detachment surgery. Bull Ophthalmol Soc Egypt 64: 483-490, 1971

28. Lazar M, Nowakowski J, Furman M, et al: Ocular penetration of topically applied mannitol. Am J Ophthalmol 70:849-851, 1970

29. Ames A, Wright RL, Kowada M, et al: Cerebral ischemia—II. The no-reflow phenomenon. Am J Pathol 52:437-453, 1968

30. Flores JE, Frega NS, DiBona DR, et al: The role of cell swelling in ischemic renal injury, *In* Friedman EA, Eliahou HE (Eds): Proc Conf Renal Failure. DHEW Publication Number (NIH) 74-608. New York, 1973, pp 19-29

31. Bernstein LM, Grossman A: Diuretic effect of mannitol in nephrotic edema. J Lab Clin Med 59:309-319, 1962

32. Gagnon O, Gertman PM, Iber FL: Comparison of oral isosorbide and intravenous mannitol as adjuncts to the diuresis of patients with cirrhosis of the liver. Am J Med Sci 254:284-295, 1967

33. Oken DE: Mannitol and the prevention of vasomotor nephropathy, *In* Giovannetti S, et al (Eds): Sixth International Congress of Nephrology. Basel, Karger, 1976, pp 578-583

34. Schroder K, Gassler U: The influence of mannitol, ethacrynic acid and furosemide on glomerular filtration in experimental acute renal failure. Postgrad Med J 47(Suppl):11-12, 1971

35. Flores J, DiBona DR, Beck CH, et al: The role of cell swelling in ischemic renal damage and the protective effect of hypertonic solute. J Clin Invest 51:118-126 1972

36. Franklin WA, Ganote CE, Jennings RB: Blood reflow after renal ischemia—Effects of hypertonic mannitol on reflow and tubular necrosis after transient ischemia in the rat. Arch Pathol 98:106-111, 1974

37. Danielson BG, Grangsjo G, Karkmark B, et al: Kidney function and intrarenal blood flow distribution after bleeding and infusions of mannitol and dextran. Acta Aesthesiol Scand 17:8-21, 1973

38. Conte NF, Gagnon JA, Barry KG: Intrinsic renal effect of hypertonic mannitol infusion (HMI) on renal clearances of PAH (C_{PAH}), exogenous creatinine (C_{CR}), and urine flow (UF) during hemorrhagic shock in dogs. Clin Res 10:247, 1962

39. Szabo G, Magyar S: Effect of hypertonic mannitol solution on circulation and renal function in acute blood loss. Acta Med Acad Sci Hung 23:325-335, 1967

40. Doberneck RC Schwartz FD, Barry KG: A comparison of the prophylactic value of 20 percent mannitol, 4 percent urea, and 5 percent dextrose on the effects of renal ischemia. J Urol 89:300-302, 1963

41. Luke RG, Briggs JD, Allison ME, et al: Factors determining response to mannitol in acute renal failure. Am J Med Sci 259:168-174, 1970

42. Sherwood T, Lavender JP, Russell SB: Mercury-induced renal vascular shut-down—Observations in experimental acute renal failure. Eur J Clin Invest 4:1-8, 1974

43. Wilson DR, Thiel G, Arce ML, et al: Glycerol induced hemoglobinuric acute renal failure in the rat—3. Micropuncture study of the effects of mannitol and isotonic saline on individual nephron function. Nephron 4:337-355, 1967

44. Powers SR, Boba A, Hostnik W, et al: Prevention of postoperative acute renal failure with mannitol in 100 cases. Surgery 55:15-23, 1964

45. Dawson J: Jaundice and anoxic renal damage—Protective effect of mannitol. Br Med J 1:810-811, 1964

46. Dawson J: Post-operative renal function in obstructive jaundice: Effect of a mannitol diuresis. Br Med J 1:82-86, 1965

47. Eliahou H: Mannitol therapy in oliguria of acute onset. Br Med J 1:807-809, 1964

48. Frega NS, DiBona DR, Leaf A: Ischemic renal injury. Kidney In 10:517-525, 1976

49. Hagstam KE, Lindergard B, Tibbling G: Mannitol infusion in regular haemodialysis treatment for chronic renal insufficiency. Scand J Urol Nephrol 3:257-263, 1969

50. Rodrigo F, Shideman J, McHugh R, et al: Osmolality changes during hemodialysis. Ann Intern Med 86:554-561, 1977

51. Anderson CF, O'Kane HO, Shorter RG, et al: Use of diuretic agents during oliguria after renal transplantation. Surgery 67:249-254, 1970

52. Taylor DA, Macken KL, Fiore AS: Mannitol pyelography: A simplification of the drip infusion technic. Radiology 88:1117-1120, 1967

53. Taylor DA, Chovnick SD, Phillips SH: The use of rapid sequence mannitol pyelography in the diagnosis of renovascular hypertension. Radiology 89:1095-1099, 1967

54. Oetliker OH, Simon J, Tietze HU: Diagnostic value of mannitol-induced diuresis in children. Acta Paediatr Scand 63: 113-121, 1974

55. Cirksena WJ, Bastain RC, Malloy JP, et al: Use of mannitol in exogenous and endogenous intoxications. N Engl J Med 270:161-166, 1964

56. Gurr FW, Scroggie JE: Eucalypus oil poisoning treated by dialysis and mannitol infusion, with an appendix on the analysis of the biological fluids for alcohol and eucalyptol. Australia Ann Med 14:238-249, 1965

57. Prowse K, Pain M, Marston AD, et al: The treatment of salicylate poisoning using mannitol and forced alkaline diuresis. Clin Sci 38:327-337, 1970

58. Adamson JS Jr, Flanigan WJ, Ackerman GL: Treatment of bromide intoxication with ethacrynic acid and mannitol diuresis. Ann Intern Med 65:749-752, 1966

59. Barry KG, Hunter RH, David TE, et al: Acute uric acid nephropathy: Treatment with mannitol diuresis and peritoneal dialysis. Arch Intern Med 111:452-459, 1963

60. Skeith MD, Healey LA, Cutler RE: Urate excretion during mannitol and glucose diuresis. J Lab Clin Med 70:213-220, 1967

61. Cvitkovic E, Spaulding J, Bethune V, et al: Improvement of cis-dichlorodiammine-platinum (NSC 119875): Therapeutic index in an animal model. Cancer 39:1357-1361, 1977

62. Hayes DM, Cvitkovic E, Golbey RB, et al: High dose cisplatinum diammine dichloride: Amelioration of renal toxicity by mannitol diuresis. Cancer 39:1372-1381, 1977

63. Polec RB, Yeh SD, Shils ME: Protective effect of ascorbic acid, isoascorbic acid and mannitol against tetracycline-induced nephrotoxicity. J Pharmacol Exp Ther 178:152-158, 1971

64. Olivero JJ, Lozano-Mendez J, Ghafary EM, et al: Mitigagation of amphotericin B nephrotoxicity by mannitol. Br Med J 1:550-551, 1975

65. Bullock WE, Luke RG, Nuttall CE, et al: Can mannitol reduce amphotericin B nephrotoxicity?—Double-blind study and description of a new vascular lesion in kidneys. Antimicrob Agents Chemother 10:555-563, 1976

66. Rosch JM, Pazin GJ, Fireman P: Reduction of amphotericin B nephrotoxicity with mannitol. JAMA 235:1995-1996, 1976

67. Bouzarth WF, Goldfedder P, Shenkin HA: Hypertonic mannitol as a treatment for complications of cerebral arteriograph. Am J Roentgen 104:119-122, 1968

68. Kindt GW, Waldman J, Kohl S, et al: Intracranial pressure in Reye syndrome—Monitoring and control. JAMA 231:822-825, 1975

69. MacCulsh AC, Munro JF, Duncan LJ: Treatment of hypoglycaemic coma with glucagon intravenous dextrose, and mannitol infusion in a hundred diabetics. Lancet 2:946-949, 1970

70. Parker AJ, Park RD, Stowater JL: Reduction of trauma-induced edema of spinal cord in dogs given mannitol. Am J Vet Res 34:1355-1357, 1973

71. Shalit MN: Effect of intracarotid artery administration of mannitol on cerebral blood flow and intracranial pressure in experimental brain edema. Isr J Med Sci 10:577-580, 1974

72. Wise BL, Chater N: The value of hypertonic mannitol solution in decreasing brain mass and lowering cerebral spinal fluid pressure. J Neurosurg 19:1038-1043, 1962

73. Shenkin HA, Goluboff B, Haft H: The use of mannitol for the reduction of intracranial pressure in intracranial surgery. J Neurosurg 19:897-901, 1962

74. Shenkin HA, Goluboff B, Haft H: Further observations on effects of abnormally increased osmotic pressure of plasma on cerebrospinal-fluid pressure in man. J Neurosurg 22:563-568, 1965

75. Richardson HD, Nakamaura S: An electron microscopic study of spinal cord edema and the effect of treatment with steroids, mannitol, and hypothermia. Proc Vet Adm Spinal Cord Inj Conf 18:10-16, 1971

76. Gjerris F, Schmidt K: Chronic subdural hematoma—Surgery or mannitol treatment. J Neurosurg 40:639-642, 1974

77. Suzuki J, Takaku A: Nonsurgical treatment of chronic subdural hematoma. J Neurosurg 33:548-553, 1970

78. Takimoto N, Watanabe M, Kinjo T, et al: Clinical study on penetration of antibiotics into cerebrospinal fluid (second report)—Study on intravenous administration of sodium cephalothin with mannitol solution. Neuro Surg (Tokyo) 5:137-143, 1977

79. Kahn DR, Cerny JC, Lee RWS, et al: The effect of dextran and mannitol on renal function during open-heart surgery. Surgery 57:676-679, 1965

80. Etherige EE, Levitin H. Nakamura K, et al: Effect of mannitol on renal function during open-heart surgery. Ann Surg 161: 53-62, 1965

81. Barry KG, Cohen A, LeBlanc PC Jr: Mannitolization—I. The prevention and therapy of oliguria associated with cross-clamping of the abdominal aorta. Surgery 50:335-340, 1961

82. Powell WJ Jr, DiBona DR, Flores J, et al: Effects of hyperosmotic mannitol in reducing ischemic cell swelling and minimizing myocardial necrosis. Circulation 53:45-49, 1976

83. Powell WJ Jr, DiBona DR, Flores J, et al: The protective effect of hyperosmotic mannitol in myocardial ischemia and necrosis. Circulation 54:603-615, 1976

84. Kloner RA, Reimer KA, Willerson T, et al: Reduction of experimental myocardial infarct size with hyperosmolar mannitol. Proc Soc Exp Biol Med 151:677-683, 1976

85. Hutton I, Curry GC, Templeton GH, et al: Influence of hypertonic mannitol on regional myocardial blood flow and ventricular performance in awake, intact dogs with prolonged coronary artery occlusion. Cardiovascular Res 9:409-419, 1975

86. Willerson JT, Weisfeldt ML, Sanders CA, et al: Influence of hyperosmolar agents on hypoxic cat papillary muscle function. Cardiovascular Res 8:8-17 1974

87. Christodoulou J, Erlandson R, Smithen C, et al: Effects of mannitol on cardiac ultrastructure and microcirculation following anoxia. Am J Physiol 229:853-860, 1975

88. Smithen C, Christodoulou J, Killip T, et al: Metabolic and hemodynamic consequences of mannitol following myocardial anoxia. Am J Physiol 229:847-852, 1975

89. Brachfeld N: Metabolic evaluation of agents designed to protect the ischemic myocardium and to reduce infarct size. Am J Cardiol 37:528-532, 1976

90. Brachfeld N, Christodoulou J, Keller N, et al: Hemodynamic, metabolic, and ultrastructural consequences of hyperosmolal mannitol after myocardial anoxia. Recent Adv Studies Cardiac Struct Metab 7:459-466, 1975

91. Powers SR Jr, Dhiraj S, Ryon D, et al: Hypertonic mannitol in the therapy of the acute respiratory distress syndrome. Ann Surg 185:619-625, 1977

92. Deshmukh MA, Shah S, Shah S, et al: Extra-amniotic mannitol for pregnancy termination (preliminary report). J Postgrad Med 22:23-25, 1976

93. Knochel JP: Hematuria in sickle cell trait: The effect of intravenous administration of distilled water, urinary alkalinization, and diuresis. Arch Intern Med 123:160-165, 1969

94. Hamburger JI, Desai P: Mannitol augmentation of I-131 uptake in the treatment of thyroid carcinoma. Metabolism 15: 1055-1058, 1966

95. Spaeth GL, Spaeth EB, Spaeth PG, et al: Anaphylactic reaction to mannitol. Arch Ophthalmol 78:583-584, 1967

96. Tunner WS, Kiser WS, Mann P: Studies on the significance of decreased serum sodium levels following the clinical use of mannitol. J Urol 94:470-474, 1965

97. Aviram A, Prau A, Czaczkes JW, et al: Hyperosmolality with hyponatremia, caused by inappropriate administration of mannitol. Am J Med 42:648-650, 1967

98. Moreno M, Murphy C, Goldsmith C: Increase in serum potassium resulting from the administration of hypertonic mannitol and other solutions. J Lab Clin Med 73:291-298, 1969

99. Silber SJ, Thompson N: Mannitol induced central nervous system toxicity in renal failure. Invest Urol 9:310-312, 1972

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Diseases of Phenylalanine Metabolism

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Continuing investigation of the system that hydroxylates phenylalanine to tyrosine has led to new insights into diseases associated with the malfunction of this system. Good evidence has confirmed that phenylketonuria (PKU) is not caused by a simple lack of phenylalanine hydroxylase. Dihydropteridine reductase deficiency as well as defects in biopterin metabolism may also cause the clinical features of phenylketonuria. Furthermore, these diseases do not respond to the standard treatment for phenylketonuria.

In 1934 the Norwegian physician and biochemist, Asbjorn Fölling described a disorder of phenylalanine metabolism which has since been called phenylketonuria or PKU. His observations led him to suspect that mentally defective persons with this disease differed biochemically from others. The reasoning, in turn, initiated an entirely new approach toward investigating the causes of mental retardation. PKU was the first disorder of amino acid metabolism for which a specific enzyme defect was established. Good evidence now exists that inborn enzymatic defects are the underlying causes of nearly 150 metabolic disorders and others very likely will be discovered. Previously considered a single enzymatic illness, the diseases of phenylalanine metabolism are now accurately recognized as a complex spectrum of disorders.

The Hydroxylating System

Fölling showed that persons with PKU have elevated levels of phenylalanine in the blood and that they excrete phenylpyruvate in their urine.[1,2] In 1947 Jervis conducted a series of experiments that gave a clearer understanding of the metabolic block and correctly identified the affected reaction in phenylketonuria.[3] Jervis administered phenylalanine to normal animals, as well as to humans, and noted a prompt increase in serum levels of tyrosine; when he gave phenylalanine to phenylketonuric patients, there was no increase in tyrosine. Therefore, he postulated that the block was in the system responsible for hydroxylating phenylalanine to tyrosine (Figure 1).[4,5] He later presented direct evidence supporting his hypothesis by showing that in a liver specimen from a phenylketonuric patient, phenylalanine was not converted to tyrosine.[6] If the system that catalyzes the hydroxylation of phenylalanine had been composed of only phenylalanine hydroxylase, Jervis's work would have adequately explained this aspect of PKU. However, in the last few years, researchers have shown that Jervis's hypothesis was grossly oversimplified. Actually, the phenylalanine hydroxylating system is complex, consisting of several essential components. The lack of any one of these can cause a malfunction of the entire system. The earliest indication of the complexity of this system was provided by Mitoma in 1956[7] and Kaufman in 1957.[8] Some years later Kaufman showed that the coenzyme biopterin also played an essential role in the reaction.[9]

Figure 2 shows the scheme for the complex hydroxylating system. Phenylalanine and tetra-

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hydrobiopterin are oxidized to tyrosine and dihydrobiopterin, respectively. Tyrosine and TPNH (nicotinamide adenine dinucleotide phosphate, reduced) mediate the reduction of the dihydrobiopterin, thereby regenerating tetrahydrobiopterin. The role of the reductase is to keep the pterin cofactor in the active tetrahydro form.

The dihydrobiopterin produced from the tetrahydrobiopterin during the hydroxylation reaction is an extremely unstable quinoid derivative.[10] Unless it is rapidly reduced back to the tetrahydro level, it rearranges by tautomerization to a more stable isomer, the 7,8 dihydrobiopterin,[10,11] which cannot be reduced by dihydropteridine reductase.[12] This compound can be brought back into the system by still another enzyme, dihydrofolate reductase.[13] This enzyme probably serves to salvage the 7,8 dihydrobiopterin that may be formed from the quinoid compound in any circumstances where the dihydropterdine reductase-catalyzed reaction is not fast enough to keep pace with the hydroxylase.[14] In addition, it has been shown that certain phospholipids, such as lysolecithin, when in the presence of tetrahydrobiopterin, can stimulate purified hydroxylase 30-fold to 50-fold.[15] A second reaction-stimulating product called phenylalanine hydroxylation-stimulating protein has been reported.[14,16,17] This protein also requires tetrahydrobiopterin as a cofactor.

To summarize, four factors are directly involved with the phenylalanine hydroxylation reaction: phenylalanine hydroxylase, dihydropteridine reductase, tetrahydrobiopterin and dihydrobiopterin. Finally, and perhaps playing a less dramatic role, is a fifth factor: dihydrofolate reductase. In addition, phospholipids and phenylalanine hydroxylase-stimulating protein appear to initiate the hydroxylating reaction in the presence of tetrahydrobiopterin.

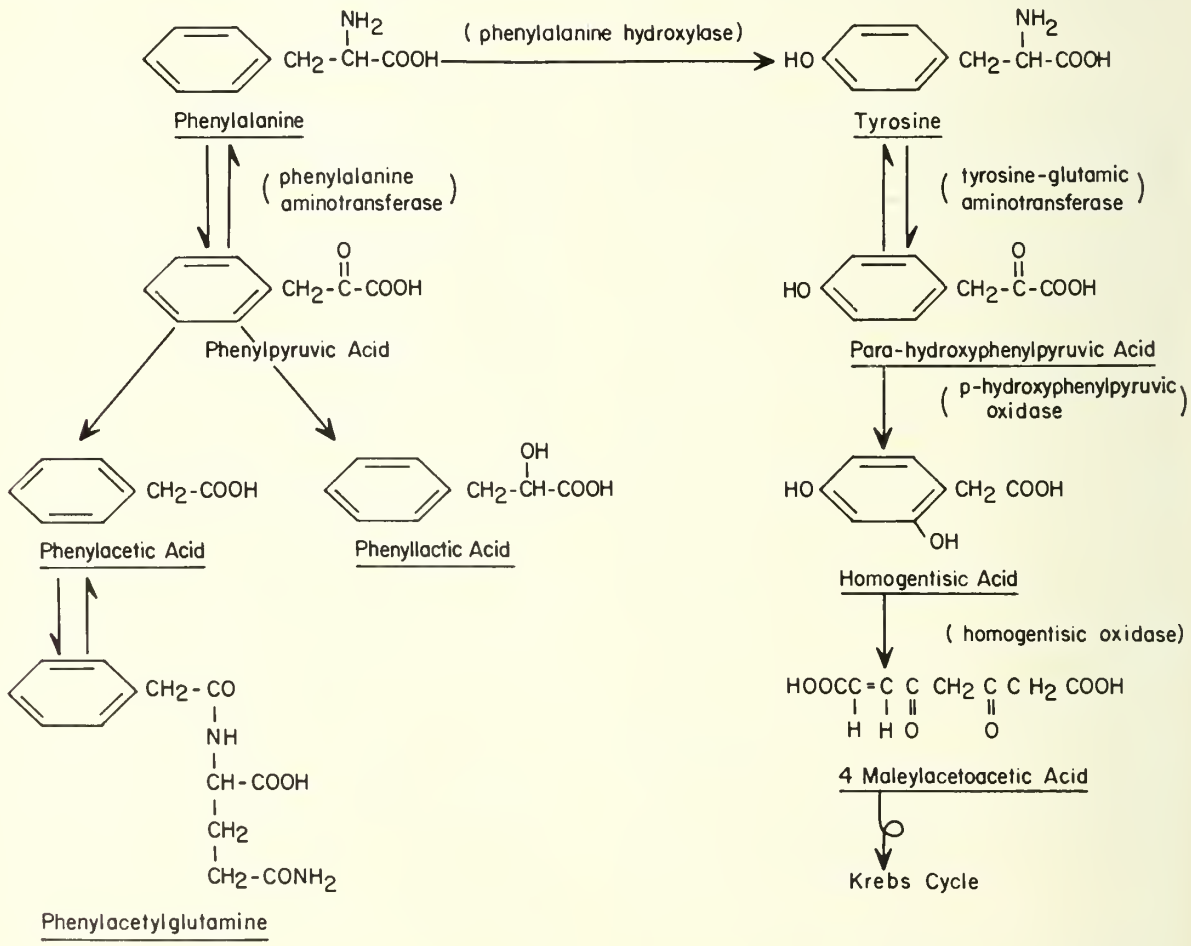

Figure 1.—A general scheme of some of the pathways of phenylalanine and tyrosine metabolism. (Adapted from Lehninger Al[4] and Koch R et al.[5])

Dihydropteridine Reductase Deficiency

There have been several reports of phenylketonuria in which neurologic deterioration has occurred despite adequate dietary restrictions to control levels of phenylalanine in the blood.[18-25] Using loading studies to determine the degree of hyperphenylalaninemia has limitations because they indicate the degree of dysfunction of the hydroxylating system as a whole, but give no indication of the function of individual components.

A child with dihydropteridine reductase deficiency will present exactly like a child with phenylalanine hydroxylase deficiency, but his or her clinical situation will continue to grow worse rather than better with dietary control of blood phenylalanine.[22] The reductase can be assayed from cultured skin fibroblasts and the procedure may be advisable in the initial diagnosis of phenylketonuria. It should be indicated in any child who is doing poorly or in whom seizures develop while on a phenylalanine-restricted diet.[24,25]

Defects in Biopterin Metabolism

Reports of defects in the metabolism of biopterin have begun to appear in the literature.[19,23] Children with this disorder have symptoms similar to those of dihydropteridine reductase deficiency, and progressive neurologic deterioration occurs in spite of adequate dietary control of phenylalanine in the blood. Biopterin derivatives from serum and urine can be measured[26] and should be considered in diagnosing unusual cases.

The same biopterin cofactor system used in the phenylalanine hydroxylation reaction is also used by neural tissue in the synthesis of the amino transmitters dopamine, norepinephrine and epinephrine, as well as in the synthesis of serotonin from tryptophan.[19,20] Therefore, a deficiency of biopterin or the enzyme dihydropteridine reductase would interfere with conversion of phenylalanine to tyrosine as well as impair production of neurotransmitters in the brain. Such a defect would be expected to cause severe neurologic disease. Phenylalanine restriction would correct the hyperphenylalaninemia without affecting the block in transmitter production, and it is unlikely to benefit the neurologic symptoms.

The Hydroxylating System in Newborn Infants

Studies on the capacity of the phenylalanine hydroxylating system of neonates have produced conflicting results. Some investigators have found that after administration of phenylalanine there is increased excretion of tyrosine in both full-term and premature neonates,[27] and that in premature infants tests may show normal phenylalanine tolerance;[28] these are consistent with an active hydroxylating system. There have been other reports of elevated levels of blood phenylalanine in premature and full-term neonates and decreased tolerance for phenylalanine in normal neonates.[29-31]

There is ample evidence that phenylalanine

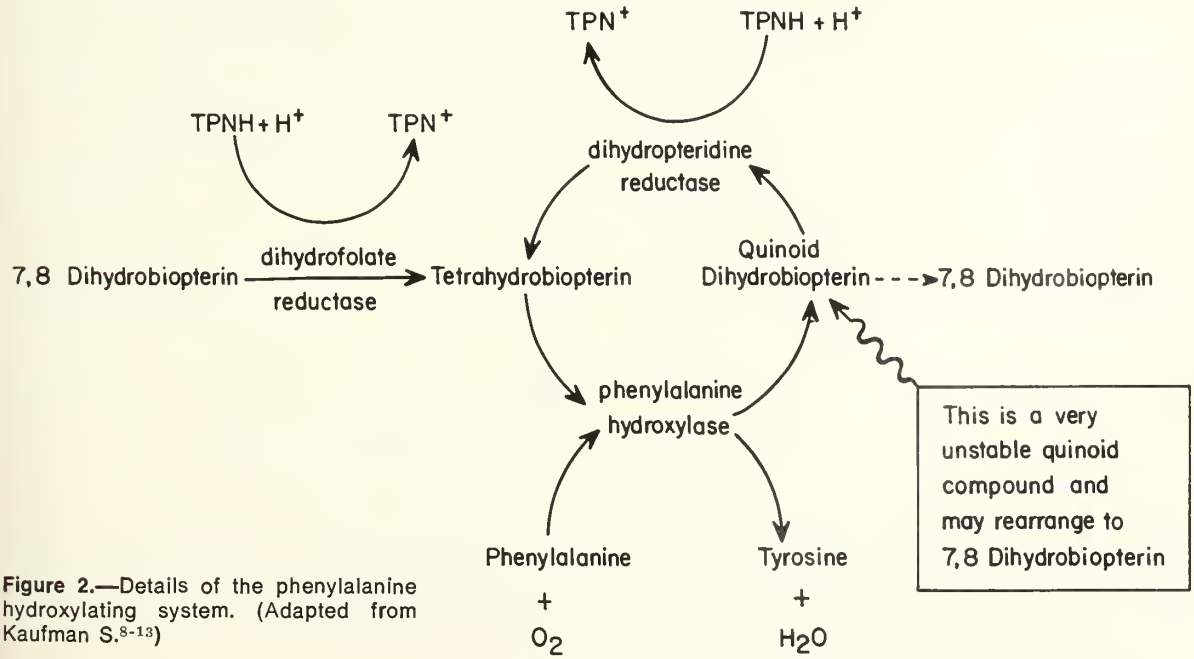

Figure 2.—Details of the phenylalanine hydroxylating system. (Adapted from Kaufman S.[8-13])

hydroxylase activity in the human liver begins at about the 8th week[32] after conception and approaches an adult level of activity at about the 13th[33,34] week; however, the activity appears to decrease in the third trimester.[35]

The Isoenzymes of Phenylalanine Hydroxylase

In the early 1960's it was discovered that the same enzyme could exist in several different forms within a single tissue. This discovery led to new information concerning the nature of enzymes, as well as enzyme changes in disease.[36] Like many other enzymes, phenylalanine hydroxylase is now known to occur in several molecular forms.

The possibility of multiple forms of phenylalanine hydroxylase was suggested in the late 1960's to explain the various types of hyperphenylalaninemia.[37-39] Bessman and Huzino were able to separate phenylalanine hydroxylase into two isoenzymes.[40] Kaufman and Fisher also reported two forms of the isoenzyme in both human and rat livers.[41-43] In 1972 Barranger and colleagues[44] described three forms of phenylalanine hydroxylase in rat liver and in 1976, Barranger characterized the three isoenzymes of phenylalanine hydroxylase (pi, kappa and upsilon) in humans as well.[45] Parker and co-workers[46] reported the results of examinations in 12 healthy adults and 10 children with classic phenylketonuria; 8 of the 12 adults had three isoenzymes; 3 had an absence of the kappa fraction, and one person was missing both pi and upsilon fractions. None of the children with classic phenylketonuria had more than 5 percent of the activity of the normal adults and no more than one isoenzyme was ever found in any of these children.[47]

Isoenzymes are the result of variation in one

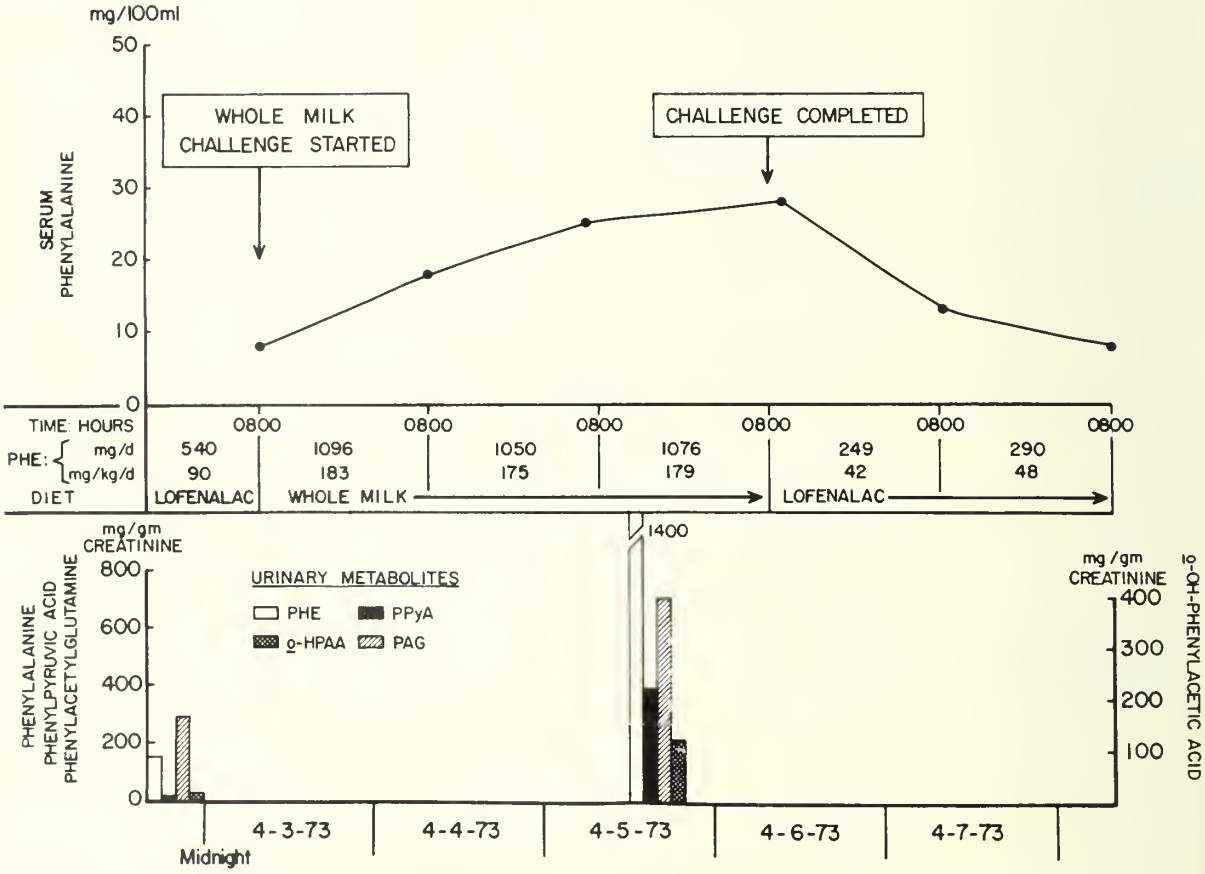

Figure 3.—A typical phenylalanine tolerance test using an oral intake of whole milk calculated to give 180 mg per kg of body weight per day of phenylalanine. Initial baseline studies of blood for serum phenylalanine and urine for phenylalanine metabolites are obtained. After challenge has begun, blood and urine specimens should be obtained every 12 hours for biochemical studies. The challenge is terminated after 72 hours. (It should be noted that in this study the serum phenylalanine level rose well above 20 mg per dl and remained there longer than 24 hours; it was accompanied by an increase of all the urinary metabolites.)

of two basic themes in protein structure, either subunit composition or amino acid sequences. Isoenzymes resulting from differences in amino acid sequences presuppose a separate and distinct mechanism for the synthesis of each form. It should be noted that such a mechanism need not be genetic or pretranscriptional in origin, but can also represent a posttranslational modification. In any event, all data at this time suggest that the isoenzymes of phenylalanine hydroxylase are three clearly different forms.[45]

Isoenzymes probably play a much more important role in explaining the wide clinical variation of the hyperphenylalaninemias[31,35,48-50] than do the extremely rare disorders, pteridine reductase and biopterin.

Definition of Phenylketonuria

The normal blood level of phenylalanine in humans is 1 to 3.5 mg per dl. Any level above 3.5 mg per dl can be called hyperphenylalaninemia. At one end of the spectrum is phenylketonuria (Fölling disease, PKU and classic PKU are synonymous terms), with its attendant mental and motor retardation. At the other end of the spectrum are the mild hyperphenylalaninemias which produce few if any detectable ill effects but which, nonetheless, should receive attention because there is evidence that few adults with elevated phenylalanine have completely normal intelligence.[51,52]

The literature is in agreement that classic phenylketonuria should be treated although, as yet, no clear definition exists.[5,53-59] Some authors refer vaguely to treating children in whom serum phenylalanine levels are greater than 25 mg per dl.[60] Others state that any child with blood phenylalanine levels greater than 15 mg per dl, especially when they are accompanied by urinary metabolites of phenylalanine, should be treated.

For purposes of consistency, we have chosen the definition used by the Collaborative Study of Children Treated for Phenylketonuria.[62] They calculate a loading dose of L-phenylalanine from a *normal* diet which is about 180 mg per kg of body weight per day. Figure 3 illustrates a typical loading study, which can be defined as follows: In two determinations, the serum phenylalanine level is 20 mg per dl or above in two blood specimens drawn at least 24 hours apart. From the same blood specimens, two determinations of serum tyrosine level show values below 5 mg per dl, accompanied by elevated levels of the metabolites of phenylalanine in the urine. In normal subjects given a single dose of L-phenylalanine, levels peak rapidly and return to the baseline within four hours. Likewise, urinary excretion of phenylalanine and its metabolites (Figure 3), phenylpyruvic acid, orthohydroxyphenyl acetic acid and phenylacetyl glutamine, increase very little in normal children.[55]

In the absence of a referral center, and if the sophisticated loading studies just described are not available, then any child with a persistent serum phenylalanine level greater than 10 mg per dl should be treated.

The term *variant* is found throughout the literature and is frequently applied to those forms of hyperphenylalaninemia that physicians do not consider to be cases of classic PKU. Unfortunately, the use of this term is often interpreted to mean that treatment is unnecessary. With the elucidation of the components of the hydroxylating system, the term variant has begun to be applied to those forms of hyperphenylalaninemia and presumably could be applied to the isoenzyme deficiencies as well. It is hoped that the term will eventually be replaced by a more specific diagnosis.

Screening

It is necessary to test newborn infants if a diagnosis is to be made before signs and symptoms appear, and in time for a low-phenylalanine diet to be most effective.[63] Screening methods originally were based on testing for the presence of phenylpyruvic acid in urine. This proved adequate for older children and adults, but inadequate for very young infants who may not begin to excrete phenylpyruvic acid for several weeks.[64,65] In addition, because phenylpyruvic acid is relatively unstable and oxidizes easily a diagnosis may be missed if the test is not done promptly.

There are many methods for determining the presence of phenylalanine in the blood.[66] A fluorometric method based on the formation of a fluorescent substance when phenylalanine is heated with ninhydrin in the presence of leucylalanine is now widely used.[67]

Paper chromatography, thin layer chromatography and gas chromatography have the advantage of showing small increases in phenylalanine as well as other amino acids; however, these methods are time consuming and appear to be impractical for mass screening programs.

The most popular method used for mass screen-

ing has been developed by Guthrie and Susi.[68] Discs are punched from filter paper that has been saturated with blood and then allowed to dry. These uniform discs are incubated on a tray of agar seeded with Bacillus subtilis and containing 3-2-thienylalanine, an inhibitor of the organism's growth. As the phenylalanine from the blood spreads from each disc onto the medium it reverses the inhibition of bacterial growth, thereby yielding an area of bacteria that can be measured and compared with that obtained from discs containing known amounts of phenylalanine. This simple, effective method is now used to screen newborn infants throughout the United States and in many parts of the world.[69]

The possibility of missing a diagnosis is greatest in neonates screened very shortly after birth.[54,70] In a study of infants in whom a diagnosis of phenylketonuria was later established, the phenylalanine concentration during the first three days of life was substantially lower than in those screened later.[70-72] It appears desirable to delay newborn screening as long as is safely possible[73] and, for those infants in whom a negative result is obtained before 3 days of age, a second test should be seriously considered at the first well-baby visit. All initial serum phenylalanine levels greater than 4 mg per dl should be further investigated.

Treatment

Reducing phenylalanine intake by dietary management has been the mainstay of therapy since Bickel and co-workers first described it in 1954.[74,75] Independently and almost simultaneously, Armstrong's group in the United States[76] and Woolf and his colleagues in London[77] also began using a low-phenylalanine diet. The goal of the diet is to reduce blood phenylalanine to acceptable clinical levels that are as near to normal as possible. Essentially, the dietary regimen includes a well-balanced amino acid mixture with either a very small amount or no phenylalanine at all. The amino acid mixture provides most of the necessary protein because the patient is not ordinarily allowed to eat high-protein foods such as meat, eggs and milk products. However, natural foods that are low in phenylalanine such as vegetables may supplement the diet. The amount of these foods allowed depends largely on each person's phenylalanine requirement.[61,78,79] The minimum level of blood phenylalanine below which treatment is unnecessary remains in question. Most physicians agree that treatment is necessary for levels above 20 mg per dl, and many clinics treat infants if their levels of phenylalanine are persistently greater than 15 mg per dl and if abnormal metabolites are present in the urine.[79,80] Children with concentrations below 10 mg per dl are usually not treated, although there is concern that there may be slight retardation associated with even these small elevations of phenylalanine, especially when they occur during the first few months of life.[81]

There are several preparations on the world market manufactured for use in managing patients requiring a low-phenylalanine diet. In the United States those most widely used are Lofenalac and the newer Product 3229,[82] both manufactured by the Mead Johnson Company. Albumaid X P,[83] is available from Ross Laboratories as PKU-aid; Aminogran, Cymogran and Minafen are amino acid mixtures made in Europe, and Lophe Milk and Phenytola are made in Japan.

Dietary treatment is not effective in those rare patients whose biochemical features result from causes other than phenylalanine hydroxylase deficiency.[21,23,24,84-87] In some cases good response to L-dopa, L-5-hydroxytryptophan and carbidopa have been reported.[23,87,88] The administration of pterin has also been suggested: however,[85,89] there is considerable concern about the efficacy of this treatment.[90]

The Collaborative Study

In 1967 a national prospective collaborative study of children treated for phenylketonuria was initiated. Its goal was to determine the effect of dietary treatment on the mental, physical and psychosocial development of children.[62,91] It was designed to overcome many of the problems of previous studies such as lack of documentation of diagnosis, laboratory variability from one clinic to another, small sample size, lack of random design, bias selection of persons placed in institutions, and bias based on the intelligence and social class of the parents.[92]

Children who were identified as having phenylketonuria were randomly assigned to one of two treatment groups. An attempt was made to maintain blood phenylalanine levels between 1.0 and 5.4 mg per dl in the first treatment group and between 5.5 and 9.9 mg per dl in the second group. The investigators have found it extremely difficult to maintain levels in the children within these arbitrary limits because these levels have

tended to drift upward. The latest report indicates that 203 children are in the study.[63]

This same publication reported the intelligence quotients of 111 of the children in the study who had reached the age of 4 years.[63] The mean Stanford Binet intelligence quotient was 93, which is slightly below the mean for the normal population, although well within one standard deviation. Furthermore, those children for whom dietary treatment was initiated during the first month of life scored a mean intelligence quotient of 95, compared with 85 for those who were initially treated at 31 to 65 days after birth. Overall, the results are encouraging, and lessen fears that the diet is harmful or ineffective.

Discontinuation of Diet

The relationship between reducing phenylalanine in the blood and minimizing mental retardation in children with phenylketonuria has been well established;[5,56,93-100] however, determining the most efficacious time to discontinue the diet remains a serious problem. Some clinicians suggest stopping the diet as early as age 4[94] or 5 while others are much more conservative.[5,102] Some investigators feel that mental deterioration occurs even in older children if blood phenylalanine levels are allowed to increase as a result of an unrestricted phenylalanine intake,[100-104] but others disagree.[79,85,105-107]

Maintaining a child who both appears *and* feels normal on a special diet for years is a heavy burden for the child and the family. Aside from financial considerations regarding maintenance of the dietary regimen, important noneconomic factors exist as well. The necessity of eating *special* food and the stress of being an outsider at parties or group activities where other children have no dietary restrictions often contribute to poor social and behavioral adjustment in these children.[98,107,108] The special diet makes meal planning difficult and can cause tension during those times the family is together. Therefore, it is beneficial to take children off the diets when safely possible. If, on the other hand, there is continued risk of mental deterioration,[109] the children should remain on treatment.

The Collaborative Study is considering the effects of discontinuing the low-phenylalanine diet by randomly selecting children for continuation or discontinuation at the age of 6 years. At present the number of children is still too small to detect pronounced differences between the two groups.[110]

Maternal Phenylketonuria

The effects of maternal phenylalanine elevation on offspring were first suggested by Dent in 1956.[111] His hypothesis has since been confirmed by the findings of numerous studies.[112-150] Early diagnosis and treatment of the disorder has produced an increasing population of women with hyperphenylalaninemia who are approaching child-bearing age; therefore, this issue has become important.

Pueschel[78] reviewed the world literature[111-150] on maternal phenylketonuria and found 61 phenylketonuric mothers who gave birth to 197 children. Of these children, 17 were phenylketonuric; however, only 32 of the 197 had normal intelligence. Eight of the 61 mothers with classic phenylketonuria had attempted or carried out some dietary treatment during part of their pregnancies. Three of these mothers gave birth to nonphenylketonuric children with normal intelligence.

At the 14th annual meeting of the Collaborative Study of Children Treated for Phenylketonuria,[110] Mabry presented an updated review of the world literature[151-170] to which we have added several cases known to us or in additional literature[171] (Table 1). The mothers were divided into two groups: those whose blood phenylalanine levels were greater than 20 mg per dl were designated as having PKU and those whose blood phenylalanine levels were less than 20 mg

TABLE 1.—*Summary of the Outcomes of Pregnancies of 87 Women With Hyperphenylalaninemia*

	PKU	*Non-PKU*	*Unexamined*	*Live Births*	*Spontaneous Abortions*	*Number of Pregnancies*	*Unexplained Infant Deaths*	*Normal IQ*	*Seizures*	*Microcephaly*	*Growth Retardation*	*Congenital Anomalies*
65	Mothers with PKU (phenylalanine levels greater than 20 mg per dl)											
	21	150	25	196	41	237	27	17	20	76	25	28
22	Hyperphenylalaninemic mothers (phenylalanine levels less than 20 mg per dl)											
	6	54	6	65	13	79	5	8	2	23	4	7
87	27	204	31	261	54	316	32	25	22	99	29	35

PKU = phenylketonuria

per dl were designated as having hyperphenylalaninemia. There were 261 live births and 10 percent of the infants from each group were phenylketonuric. There were 41 spontaneous abortions and 27 unexplained infant deaths in the PKU group representing a loss of 29 percent. In the hyperphenylalaninemic group there were 5 unexplained infant deaths and 13 spontaneous abortions which represented a loss of 23 percent. Of extreme concern was the high percentage of microcephalic children born to this group of mothers. Only 9 percent of the children in the PKU group and 12 percent of those born to hyperphenylalaninemic mothers had normal intelligence. Of the eight women in the PKU group who were receiving dietary treatment for the last half of their pregnancies,* three had normal children. One of the hyperphenylalaninemic mothers was treated from the 21st to the 39th week of her gestation[140] and she gave birth to a normal child. Although this is encouraging, it does not provide evidence that a diet restricted in phenylalanine is sufficient to produce intellectually normal children.

In addition, there is growing evidence that heterozygous asymptomatic mothers may provide unfavorable circumstances for normal fetal development.[172-175] Bessman[176] has proposed that genetic deficiencies in nonessential amino acid synthesis may be important causes of mental retardation. He postulates that a person who is genetically deficient in the synthesis of any of the 12 nonessential amino acids, nevertheless requires that amino acid in the diet just as a healthy person requires any essential amino acid. Because the late stage of fetal development is the period when the brain grows most rapidly, and because a deficiency in any single amino acid causes diminished protein synthesis, Bessman proposes that mental retardation occurs during this time because a heterozygote mother is unable to deliver an appropriate amount of the nonessential amino acid (tyrosine in this case) to her fetus that, in turn, is unable to correct for the deficiency due to its own genetic constitution. Supplementing the diets of heterozygous phenylketonuric mothers with tyrosine has been suggested as a way of solving this problem.

Identification of Heterozygotes for Phenylketonuria

It would be useful to be able to identify heterozygotes for PKU. Many systems have been proposed using loading studies or serum levels of phenylalanine, or both, under controlled conditions.[177-180] Although complete discrimination between heterozygotes may not be achieved,[181] the methods are sufficiently sensitive to give a high probability of discrimination between homozygotes and heterozygotes, which is useful in counseling. In addition, liver biopsies can be used for direct enzyme assay.

Anomalies

The occurrence of major anomalies in infants born in a normal population has been estimated at 2 percent and the incidence of at least one minor anomaly at 14.7 percent.[182] Johnson and co-workers,[183] reporting on 150 cases of phenylketonuria, found an overall incidence of anomalies of 9.3 percent, a rate which is not substantially different from that found in the general population. The only exception was an increased incidence of pyloric stenosis which has previously been noted.[184,185] The high incidence rate suggests that infants with pyloric stenosis should be considered for a repeat serum phenylalanine test. The high incidence also indicates a need for physicians to consider the possibility of various metabolic diseases such as hyperphenylalaninemia when evaluating neonates with excessive vomiting.

Phenylketonuria has been reported in conjunction with a variety of disorders including the Down syndrome,[186,187] the Klinefelter syndrome,[188] megacolon,[189,190] scleroderma[191,192] and Fahr disease.[24] It has also occurred with other genetic diseases: neurofibromatosis,[193] hypophosphatasia,[194] familial hypercalcemia,[195] cystathioninuria,[196] muscular dystrophy,[197,198] hyperammonemia[199] and Schilder leukodystrophy.[200] Neuronal lipofuscin lipidosis[201] and alpha-hydroxybutyric aciduria[202] have been reported in patients with biochemical features of phenylketonuria. Whether these represent a coincidence in the presence of two disorders or whether, like dihydropteridine reductase deficiency, these conditions produce biochemical features similar to those of phenylketonuria, is unknown.

The Team Approach

Hyperphenylalaninemia states are rare, and a practicing physician may never encounter a form of the disorder in his lifetime. The diagnosis of the many states of hyperphenylalaninemia is difficult to make and dietary management is time consuming. Therefore, a team approach in treatment

*References 121, 130, 139, 148, 149, 158, 163, 165

is highly recommended.[5,107,206] Ideally, a psychologist should be available for testing,[203] as well as a counselor to assist the family.[204] A qualified dietitian familiar with the phenylalanine content of various foods is essential.[61,79,205] University centers are often better equipped to treat hyperphenylalaninemia. Four or five children may be examined in a single day and sophisticated laboratory procedures are available for diagnosis and follow-up. To be sure, phenylketonuric children also contract the same illnesses as other children and require the same type of primary care as do the others. Thus, for optimal medical care, the specialty clinic should maintain good communication with primary care physicians to assure the best possible continuity of treatment.

Pathophysiology

Phenylalanine ingested in food is distributed in three ways: it is used directly for body protein synthesis, is metabolized or it remains in the free amino acid pool in the blood, plasma and tissues.[207] The amount of phenylalanine used for protein synthesis varies considerably with age, although it has been shown that protein synthesis from phenylalanine in phenylketonuria is similar to that in nonphenylketonuric persons.[208]

The major pathway in metabolism of phenylalanine is formation of tyrosine by hydroxylation (Figure 1). With dysfunction of this reaction there is a great increase in the substances that result from alternate pathways of phenylalanine metabolism such as phenylpyruvic acid, phenylacetic acid and phenyllactic acid. A toxic mechanism has long been suspected as playing a role in the pathogenesis of phenylketonuria. Clinical observations tend to confirm that a toxic effect influences the somatic and central nervous system functions which are responsive to changes in the level of phenylalanine intake.[5,53,55,56,209,210]

The concentration of phenylalanine in the free amino acid pool is increased in the presence of phenylketonuria.[211] Of particular interest is that a high concentration of phenylalanine is also associated with disturbances in cerebral serotonin catecholamine metabolism[212] and may cause hypervolemia[213] and, possibly, hypoglycemia.[214]

The biochemistry and its pathogenic implications are well reviewed by Lutz[207] and Brady.[215] Although many facts have accumulated concerning the interdependence of single metabolites, the problem of whether there is a key reaction which explains the brain damage is still unresolved.

The permanent nature of impairment in untreated patients affected with phenylketonuria has led to a search for damage to structural elements of the brain. The most consistent pathologic feature in untreated phenylketonuria has been moderate reduction in the weight of the brain,[216] which is in keeping with the well-known frequency of microcephaly.[217-218] This finding has been reversed with treatment where microcephaly is not the expected diagnosis.[5,56,59,82,83,109,219]

Much attention has been given to the formation of myelin. The implication is that a metabolic defect causes interference with the proper formation of myelin or myelin proteins. It is known that phenylalanine can interfere with myelin protein under certain experimental conditions;[220,221] however, this concept may be overused because only small focal areas of demyelination have been found consistently in phenylketonuric patients.[217]

It has recently been noted that heterozygotes for the PKU trait, who have never had elevated phenylalanine levels, frequently present with intelligence quotients below normal.[210,222] Thalhammer and colleagues[210] pointed out that tyrosine levels are normal in these persons. They speculated that the genes for PKU may have some direct role in the growth of brain cells, and thereby influence intellectual development by means other than elevation of phenylalanine levels in the blood.

Conclusion

New information concerning the biochemistry of phenylalanine metabolism has accumulated over the past few years, yet the cause of mental retardation in untreated classic phenylketonuria remains obscure. Although mental retardation is not an expected outcome, several studies show that even in carefully treated patients intellectual development may be several intelligence quotient points lower than expected. Whether this represents an effect of low levels of phenylalanine or its metabolites or some genetic influence on intellectual development remains unclear.

An elevated level of serum phenylalanine is indicative of a diagnosis of phenylketonuria; however, loading studies are necessary to confirm the diagnosis. Children with phenylalanine levels consistently above 10 mg per dl should be treated until clinically acceptable levels are reached.

Current information about phenylalanine metabolism indicates that the defect in about 3 percent of all apparent classic phenylketonuria is, in

fact, due to dihydropteridine reductase or biopterin deficiency. Clinically, these varieties can not be distinguished; however, hypotonicity, convulsions and continued deterioration during adequate dietary therapy suggest this diagnosis.

The chance of missing a diagnosis of phenylketonuria is greatest in neonates; therefore, it is desirable to screen newborn infants as late as possible before they are discharged from hospital.[223] For those babies in whom results were negative before 3 days of age, a second determination of the phenylalanine level should be done at the first well-baby visit.

The isoenzymes of phenylalanine hydroxylase tend to complicate the situation further, although isoenzyme activation may explain why some neonates present with classic phenylketonuria at 3 weeks of age, but at a year have a tolerance test showing only mild hyperphenylalaninemia. Isoenzymes may also play a role in the high percentage of affected offspring from persons with hyperphenylalaninemia as well as phenylketonuria.

Because there is increased incidence of pyloric stenosis in those with phenylketonuria, infants with excessive vomiting or proved pyloric stenosis should have a repeat examination of levels of phenylalanine in the blood.

The problem of when to discontinue a low-phenylalanine diet is still unsettled. Some investigators recommend stopping at age 4 to 5 years; others recommend continuing the diet throughout the patient's lifetime. Most physicians now agree that the special diet should not be stopped before the age of 6 years.

Probably of greatest concern is maternal hyperphenylalaninemia. Most children born to mothers with this disorder are mentally retarded. Dietary restriction of phenylalanine and supplementation with tyrosine is the only treatment available, and its effectiveness remains to be confirmed.

REFERENCES

1. Fölling A: Uber Ausscheidung von Phenylbrenztraubensaure in den Harn als Stoffwechselanomalie in Verbindung mit Imbezillität. Hoppe-Seylers Z Physiol Chem 227:169-178, 1934

2. Fölling A, Close K: Uber das Vorkommen von L-phenylalanin in Harn und Blut bei imbecillitas Phenylpyruvica. Hoppe-Seylers Z Physiol Chem 254:115-116, 1938

3. Jervis GA: Studies on phenylpyruvic oligophrenia: The position of metabolic error. J Biol Chem 169:651-656, 1947

4. Lehninger AI: Oxidative degradation of amino acids, *In* Biochemistry, New York, Worth Publishers, Inc., 1970, p 442

5. Koch R, Shaw KNF, Acosta PB, et al: An approach to management of phenylketonuria. J Pediatr 76:815-828, 1970

6. Jervis GA: Deficiency of phenylalanine oxidizing system. Proc Soc Exper Biol Med 82:514-515, 1953

7. Mitoma C: Studies on partially purified phenylalanine hydroxylase. Arch Biochem 60:476-484, 1956

8. Kaufman S: The enzymatic conversion of phenylalanine to tyrosine. J Biol Chem 226:511-524, 1957

9. Kaufman S: The structure of the phenylalanine-hydroxylation cofactor. Proc Natl Acad Sci (Wash) 50:1085, 1963

10. Kaufman S: Studies on the structure of the primary oxidation products formed from tetrahydropteridines during phenylalanine hydroxylation. J Biol Chem 239:332-338, 1964

11. Kaufman S, Max EE: Studies on the phenylalanine hyroxylating in human liver and their relationship to pathogenesis of PKU and hyperphenylalaninemia, *In* Bickel H, Hudson FP, Woolf LI (Eds): Phenylketonuria and Some Other Inborn Errors of Amino Acid Metabolism. Stuttgart, Georg Thieme Verlag, 1971, pp 11-19

12. Kaufman S: Studies on the mechanism of the enzymatic conversion of phenylalanine to tyrosine. J Biol Chem 234:2677-2682, 1959

13. Kaufman S: Metabolism of the phenylalanine hydroxylation cofactor. J Biol Chem 242:3934-3943, 1967

14. Kaufman S: The phenylalanine hydroxylating system in phenylketonuria and its variants. Biochem Med 12:42-54, 1976

15. Fisher DB, Kaufman S: The stimulation of rat liver phenylalanine hydroxylase by lysolecithin and α-chymotrypsin. J Biol Chem 248:4345-4353, 1976

16. Huang CY, Max EE, Kaufman S: Purification and characterization of phenylalanine hydroxylase-stimulating protein from rat liver. J Biol Chem 248:4235-4241, 1973

17. Huang CY, Kaufman S: Studies on the mechanism of action of phenylalanine hydroxylase and its protein stimulator. J Biol Chem 248:4242-4251, 1973

18. Bartholome K: A new molecular defect in phenylketonuria. Lancet 2:1580, 1974

19. Smith I, Clayton BE, Wolf OH: New variant or phenylketonuria with progressive neurological illness unresponsive to phenylalanine restriction. Lancet 1:1108-1111, 1975

20. Kaufman S, Milstien S, Bartholome K: New forms of phenylketonuria. Lancet 2:708, 1975

21. Butler IJ, Holtzman NA, Kaufman S, et al: Phenylketonuria due to deficiency of dihydropteridine reductase. Pediatr Res 9:348, 1975

22. Kaufman S, Holtzman NA, Milstien S, et al: Phenylketonia due to a deficiency of dihydropteridine reductase. N Engl J Med 293:785-789, Oct 16, 1975

23. Leeming RJ, Blair JA, Rey F: Biopterin derivatives in atypical phenylketonuria. Lancet 1:99-100, 1976

24. Parker CE, Landing BH: Coincidence of Fahr disease and phenylketonuria. J Pediatr 91:273-276, 1977

25. Bartholome K, Byrd DJ, Kaufman S, et al: Atypical phenylketonuria with normal phenylalanine hydroxylase and dihydropteridine reductase activity in vitro. Pediatrics 59:757-761, 1977

26. Leeming RJ, Blair JA, Milikian V, et al: Biopterine derivatives in human body fluids and tissues. J Clin Path 29:444-451, 1976

27. Levin SZ, Dann M, Marples E: A defect in the metabolism of tyrosine and phenylalanine in premature infants—Demonstration of the irreversible conversion of phenylalanine to tyrosine in the human organism. J Clin Invest 22:551-562, 1943

28. Menkes JH, Avery ME: The metabolism of phenylalanine and tyrosine in the premature infant. Bull Johns Hopkins Hosp 113:301-319, 1963

29. Hsia DYY, Litwack M, O'Flynn ME, et al: Serum phenylalanine and tyrosine levels in the newborn infant. N Engl J Med 267:1067-1070, 1962

30. LaDu BN, Howell RR, Michael PJ, et al: A quantitative micromethod for the determination of phenylalanine and tyrosine and its application in the diagnosis of phenylketonuria in infants. Pediatrics 31:31-39, 1923

31. Bremer HJ, Neumann W: Phenylalanine-Toleranz bei fruhgeborenen reifen Neugeboren, Sauglingen und Erwachsenen. Klin Wschr 44:1076-1081, 1966

32. Friedman PA, Kaufman SA: A study of the development of phenylalanine hydroxylase in the fetuses of several mammalian species. Arch Biochem Biophys 146:321-326, 1971

33. Jakubovic A: Phenylalanine hydroxylating system in the human fetus at different developmental ages. Biochem Biophys Acta 237:469-475, 1971

34. Raiha NCR: Phenylalanine hydroxylase in human liver during development. Pediatr Res 7:1-4, 1973

35. Bessman SP, Wapnir RA, Towell MC: Development of liver phenylalanine hydroxylase and brain aromatic hydroxylases in human fetuses. Biochem Med 17:1-7, 1977

36. Zinkham WH, Blanco A, Kupchyk L: Isoenzymes: Biological and clinical significance. Pediatrics 37:120-130, 1966

37. Auerbach VH, DiGeorge AM, Carpenter GC, ch 2, *In* Nyhan WL (Ed): Amino Acid Metabolism and Genetic Variation. New York, McGraw Hill, 1967, pp 11-68

38. Woolf LI, Granston WI, Goodwin BL: Genetics of phenylketonuria. Nature 213:882-883, 1967

39. Woolf LI, Goodwin BL, Cranston WI, et al: A third allele at the phenylalanine hydroxylase locus in mild phenylketonuria (hyperphenylalaninemia). Lancet 1:114-117, 1968

40. Bessman SP, Huzino A: Phenylalanine hydroxylase—New components of the rat liver system. Fed Proc 28:408, 1969

41. Kaufman S, Fisher DB: Purification and some physical properties of phenylalanine hydroxylase from rat liver. J Biol Chem 245:4745-4750, 1970

42. Connelan JM, Danks DM: Demonstration of two forms of phenylalanine hydroxylase in human liver obtained at autopsy. Biochimet Biophy Acta 293:48-55, 1973

43. Gillam SS, Woo SLC, Woolf LI: The isolation and properties of phenylalanine hydroxylase from rat liver. J Biochem 139:731-739, 1974

44. Barranger JA, Geiger PS, Huzino A, et al: Isoenzymes of phenylalanine hydroxylase. Science 175:903-905, 1972

45. Barranger JA: The implications of multiple forms of phenylalanine hydroxylase in phenylketonuria and related diseases of phenylalanine metabolism. Biochem Med 15:55-86, 1976

46. Parker CE, Barranger J, Newhouse R, et al: The isoenzymes of phenylalanine hydroxylase in humans. Ann Clin Biochem 14:122-123, 1977

47. Parker CE, Barranger J, Newhouse R, et al: Studies of the isoenzymes of phenylalanine hydroxylase in humans. Biochem Med 17:8-12, 1977

48. Justice P, O'Flynn ME, Hsia DYY: Phenylalanine hydroxylase activity in hyperphenylalaninemia. Lancet 1:928, 1967

49. O'Flynn ME, Tillman P, Hsia DYY: Hyperphenylalaninemia without phenylketonuria. Am J Dis Child 113:20-30, 1967

50. Cunningham GC, Day RW, Berman JL, et al: Phenylalanine tolerance tests in families with phenylketonuria and hyperphenylalaninemia. Am J Dis Child 117:622-635, 1969

51. Levy HL, Karolkewicz V, Houghton SA, et al: Screening the "normal" population in Massachusetts for phenylketonuria. N Engl J Med 282:1455-1458, 1970

52. Levy HL, Shih VS, Karolkewicz V, et al: Persistent mild hyperphenylalaninemia in the untreated state—A prospective study. N Engl J Med 285:424-429, 1971

53. Yu JS: Phenylketonuria: A review. Postgraduate Med J 46:430-446, 1970

54. Buist NRM, Jhaveri MB: A guide to screening newborn infants for inborn errors of metabolism. Fetal and Neonatal Med 82: 511-522, 1973

55. Blaskovics ME, Schaeffler GE, Hack S: Phenylalaninemia: Differential diagnosis. Arch Dis Child 49:835-843, 1974

56. Robertson EF, Hill GN, Cashel K, et al: Management of phenylketonuria—South Australian experience of 13 cases. Med J Aust 1:647-650, 1976

57. Blaskovics ME, Nelson TL: Phenylketonuria and its variations—A review of recent developments. Calif Med 115:42-57, Jul 1971

58. Advisory Committee on Inborn Errors of Metabolism to the Ontario Ministry of Health: Phenylketonuria variants in Ontario. Can Med Assoc J 115:509-512, 1976

59. Berry HK: Hyperphenylalaninemias and tyrosinemias. Clin Perinatol 3:15-40, 1976

60. Blaskovics ME, Shaw KNF: Hyperphenylalaninemia: Methods for differential diagnosis, *In* Bickel H, Hudson FP, Woolf LI (Eds): Phenylketonuria and Some Other Inborn Errors of Amino Acid Metabolism. Stuttgart, Georg Thieme Verlag, 1971, pp 98-192

61. Clayton BE: The principles of treatment by dietary restriction as illustrated by phenylketonuria, *In* The Treatment of Inherited Metabolic Disease. St. Loenardgate, Lancaster, Lancs, England, Medical and Technical Publishing Co. Ltd, 1975, pp 1-32

62. Williamson ML, Dobson JC, Koch R: Collaborative study of children treated for phenylketonuria: Study design. Pediatrics 60:815-821, 1977

63. Dobson JC, Williamson ML, Azen C, et al: Intellectual assessment of 111 four-year-old children with phenylketonuria. Pediatrics 60:822-827, 1977

64. Armstrong MD, Centerwall WR, Horner FA, et al: The development of biochemical abnormalities in phenylketonuric infants, *In* Folch PJ (Ed): Clinical Pathology of the Nervous System. New York, Pergamon Press, Inc., 1961

65. Armstrong MD, Low MI: Phenylketonuria VIII—Relation between age, serum phenylalanine level and phenylpyruvic acid excretion. Proc Soc Exp Biol Med 94:142

66. Shaw KNF, Gortalowski MJ, Analytical methods in phenylketonuria—Clinical biochemistry, *In* Bicket H, Hudson FP, Woolf LI (Eds): Phenylketonuria and Some Other Inborn Errors of Amino Acid Metabolism. Stuttgart, Georg Thieme Verlag, 1971, pp 47-56

67. McCaman MW, Robins E: Fluorimetric method for the determination of phenylalanine in serum. J Lab Clin Med 59:885-890, 1962

68. Guthrie R, Susi A: A simple phenylalanine method for detecting phenylketonuria in large population of newborn infants. Pediatrics 32:338-343, 1963

69. Guthrie R: Mass screening for genetic disease. Hosp Prac 1:93-100, 1972

70. Holtzman NA, Meek AG, Mellits ED: Neonatal screening for phenylketonuria—IV. Factors influencing the occurrence of false positives. Am J Public Health 64:775-779, 1974

71. Holtzman NA, Meek AG, Millits ED, et al: Neonatal screening for phenylketonuria—3. Altered sex ratio; extent and possible cause. J Pediatr 85:175-181, 1974

72. Holtzman NA, Mellits ED, Kallman C: Neonatal screening for phenylketonuria—II. Age dependence of initial phenylalanine in infants with PKU. Pediatrics 53:353-357, 1974

73. Holtzman NA, Meek AG, Mellitis ED: Neonatal screening for phenylketonuria—I. Effectiveness. JAMA 229:667-670, 1974

74. Bickel H, Gerrard J, Hickmans EM: Influence of phenylalanine intake on phenylketonuria. Lancet 2:812-813, 1953

75. Bickel H, Gerrard J, Hickman EM: The influence of phenylalanine intake on the chemistry and behavior of a phenylketonuric child. Acta Pediat 43:64-77, 1954

76. Armstrong MD, Tyler FH: Studies on phenylketonuria—I. Restricted phenylalanine intake in phenylketonuria. J Clin Invest 34:565-580, 1955

77. Woolf LI, Griffiths R, Moncrieff A: Treatment of phenylketonuria with a diet low in phenylalanine. Br Med J 1:57-64, 1955

78. Pueschel SM, Hum C, Andrews M: Nutritional management of the female with phenylketonuria during pregnancy. Am J Clin Nutr 30:1153-1161, 1977

79. Acosta PB, Wenz E, Williamson M: Methods of dietary inception in infants with PKU. J Am Diet Assoc 72:164-169, 1978

80. Neil RM, Buist MB, Jhaveri BM: A guide to screen new born infants for inborn errors of metabolism. J Pediatr 82:511-522, 1973

81. Dobson JC, Kushida E, Williamson M, Friedman EG: Intellectual performance of 36 phenylketonuric patients and their nonaffected siblings. Pediatrics 58:53-57, 1976

82. Parker CE, Shaw KNF, Mitchel JB, et al: Clinical experience in dietary management of phenylketonuria with a new phenylalanine-free product. J Pediatr 19:941-943, 1977

83. Berry HK, Sutherland BS, Hunt MM, et al: Treatment of children with phenylketonuria using a phenylalanine-free protein hydrolysate (albumaid x P). Am J Clin Nutr 29:351-357, 1976

84. Kaufman S, Milstien S, Bartholome K: New forms of phenylketonuria. Lancet 2:708, 1975

85. Smith I, Clayton BE, Wolff OH: New variant of phenylketonuria with progressive neurologic illness unresponsive to phenylalanine restriction. Lancet 1:1108-1111, 1975

86. Taylor D, Hochstein P: Potential variants of phenylketonuria. Lancet 1:1378, 1975

87. Bartholome K, Byrd DJ, Kaufman S, et al: Atypical phenylketonuria with normal phenylalanine hydroxylase and dihydropteridine reductase activity in vitro. Pediatrics 59:757-761, 1977

88. Bartholome K, Byrd DJ: L-dopa and 5-hydroxytryptophan therapy in phenylketonuria with normal phenylalanine hydroxylase activity. Lancet 2:1042-1043, 1975

89. Danks DM, Cotton RGH, Schlesinger P: Tetrahydrobiopterin treatment of variant form of phenylketonuria. Lancet 2:1043, 1975

90. Kaufman S: Pterin administration as therapy for PKU due to dihydropteridin reductase deficiency. Lancet 2:767, 1975

91. Koch R, Dobson JC, Blaskovics M, et al: Collaborative study of children treated for phenylketonuria, *In* Seakins JWT, Saunders RA, Toothhill C (Eds): Treatment of Inborn Errors of Metabolism: Current Treatment and Future Prospects. Proceedings of the Tenth Symposium of the Society for the Study of Inborn Errors of Metabolism. Edinburgh & London, Churchill Livingston, 1973

92. Williamson MW, Dobson JC, Koch R: Collaborative study of children treated for phenylketonuria: Study design. Pediat 60: 815-821, 1977

93. Johnson CF: What is the best age to discontinue the low phenylalanine diet in phenylketonuria? Clin Pediat 2:148-156, 1972

94. Hudson FP: Termination of dietary treatment of phenylketonuria. Arch Dis Child 42:198-200, 1967

95. Holtzman NA, Welcher DW, Mellits ED: Termination of restricted diet in children with phenylketonuria—A randomized controlled study. N Engl J Med 293:1121-1124 1975

96. Hudson FP, Mordaunt VL, Leahy I: Evaluation of treatment begun in first three months of life in 184 cases on phenylketonuria. Arch Dis Child 45:5-12, 1970

97. Kang ES, Collee ND, Gerald PS: Results of treatment and termination of the diet in phenylketonuria (PKU). Pediatrics 46: 881-890, 1970

98. Berman JL: Phenylketonuria. Am Fam Physician 3:112-120, 1971

99. Smith I, Wolff OH: Natural history of phenylketonuria and influence of early treatment. Lancet 2:540-544, 1974

100. Brown ES, Warner R: Mental development of phenylketonuric children on or off diet after the age of six. Psychol Med 6:287-296, 1976

101. Cabalska B, Duczynska N, Borzymowska J, et al: Termination of dietary treatment in phenylketonuria. Europ J Pediatrics 126:253-262, 1977

102. Bickel H. Kaiser-Brubel S: Uber die Phenylketonurie. Deutsch Med Wochenschr 96:1415-1423, 1971

103. Cabalska B, Duczynska N, Golabek B, et al: Tentative Criteria for Terminating the Low-Phenylalanine Diet in PKU. Third Congress of the International Association for the Scientific Study of Mental Deficiency. The Hague, Netherlands, 1975

104. Smith I: The effect on intelligence of stopping the low-phenylalanine diet in children with phenylketonuria. Ann Clin Biochem 14:134, 1977

105. Hackney 1M, Hanley WB, Davidson W, et al: Phenylketonuria: Mental development, behavior and termination of low phenylalanine diet. J Pediatr 72:5:646-655, 1968

106. Frankenburg WK, Goldstein AD, Olson CO: Behavioral consequences of increased phenylalanine intake by phenylketonuric children: A pilot study describing a methodology. Am J Ment Defic 77:5:524-532, 1973

107. Beckner AS, Centerwall WR, Holt L: Effects of rapid increase of phenylalanine intake in older PKU children. J Am Diet Assoc 69:148-151, 1976

108. Robertson EF, Hill GN, Cashel K, et al: Management of phenylketonuria—South Australian experience of 13 cases. Med J Aust 1:647-650, 1976

109. Koff E, Boyle P, Pueschel SM: Perceptual-motor functioning in children with phenylketonuria. Am J Dis Child 131: 1084-1087, 1977

110. Collaborative Study of Children Treated for Phenylketonuria—Fourteenth Conference. Stateline, Nevada, Mar 14-15, 1978

111. Dent CE: Discussion of Armstrong MD: Relation of biochemical abnormality to development of mental defect in phenylketonuria, *In* Ross Laboratories: Etiologic Factors in Mental Retardation. Report of Twenty-third Ross Pediatric Research Conference November 8-9, 1956, Columbus, Ohio

112. Jervis GA: Phenylpyruvic oligophrenia: Introductory study of fifty cases of mental deficiency associated with excretion of phenylpyruvic acid. Arch Neurol Psychiatry 38:944-963, 1937

113. Jervis GA: Genetics of phenylpyruvic oligophrenia. J Ment Sci 85:719-763, 1939

114. Jervis GA: Phenylpyruvic oligophrenia (phenylketonuria). Assoc Res Nerv Dis Proc 33:259-282, 1954

115. Woolf LI, Ounsted C, Lee D, et al: Atypical phenylketonuria in sisters with normal offspring. Lancet 2:464-465, 1961

116. Partington MW: Variations in intelligence in phenylketonuria. Can Med Assoc J 86:736-743, 1962

117. Mabry CC, Denniston JC, Nelson TL, et al: Maternal phenylketonuria: Cause of mental retardation in children without metabolic defect. N Engl J Med 269:1404-1408, 1963

118. Coffelt RW: Unexpected findings from a PKU newborn screening program (Letter). Pediatrics 34:889-890, 1964

119. Richards BW: Maternal phenylketonuria. Lancet 1:829, 1964

120. Montenegro JE, Castro GL: Fenilcetonuria materna: Anomalias en la descendenc. Acta Med Venez 12:233-236, 1965

121. Forbes NP, Shaw KNF, Koch R, et al: Maternal phenylketonuria. Nurs Outlook 14:40-42, 1966

122. Perry TL, Tischler B: Phenylketonuria in a woman of normal intelligence and her child. N Engl J Med 274:1018-1019, 1966

123. Fisch RO, Walker WA, Anderson JA: Prenatal and postnatal developmental consequences of maternal phenylketonuria. Pediatrics 37:979-986, 1966

124. Mabry CC, Denniston JC, Coldwell JG: Mental retardation in children of phenylketonuric mothers. N Engl J Med 275: 1331-1336, 1966

125. Lund E, Ovnbol A: Occult phenylketonuria: Experience with the Guthrie test. Acta Path Microbiol Scand 67:9-14, 1966

126. Stevenson RR, Huntley CC: Congenital malformations in offspring of phenylketonuric mothers. Pediatric 40:33-35, 1967

127. DeMenibus CH, Graic F, Lemonnier A, et al: Children born to phenylketonuric mothers. Ann Pediatr 43:478-482, 1967

128. Colombo JP, Vassella F, Hambel R, Rossi E: Phenylketonuria, a family study: Borderline intelligence in two siblings with mentally retarded children. Helv Paediatr Acta 22:243-251, 1967

129. Frankenburg WK, Duncan BR, Coffelt RW, et al: Maternal phenylketonuria: Implications for growth and development. J Pediatr 73:560-570, 1968

130. Allan JD, Brown JK: Maternal phenylketonuria and foetal brain damage—An attempt at prevention by dietary control, *In* Holt KS, Coffey VP (Eds): Some Recent Advances in Inborn Errors of Metabolism. Edinburgh/London, E & S Livingstone 1968, pp 14-38

131. Williams R: Maternal phenylketonuria. Med J Aust 2:216-219, 1968

132. Onisaw AJ, Suzuki Y, Makamura N, et al: A phenylketonuric mother without mental retardation and her two phenylketonuric children. Pediatr Jap 15:17-21, 1968

133. Fisch RO, Doeden D, Lamsky LL, et al: Maternal phenylketonuria: Detrimental effects on embryogenesis and fetal development. Am J Dis Child 118:847-858, 1969

134. Cohen BE, Szeinberg A, Berman W, et al: Mental retardation in a family with phenylketonuria and mild hyperphenylalaninemia. Pediatrics 44:655-660, 1969

135. Hansen H: Epidemiological considerations on maternal hyperphenylalaninemia. Am J Ment Defic 75:22-26, 1970

136. Hooft C, Carton D, Broekaert E, et al: Children of phenylketonuric mothers. Acta Paediatr Belg 24:5-18, 1970

137. Levy HL, Karolkewicz V, Houghton SA, et al: Screening the "normal" population in Massachusetts for phenylketonuria. N Engl J Med 282:1455-1458, 1970

138. Yu JS, O'Halloran MT: Atypical phenylketonuria in a family with a phenylketonuric mother. Pediatrics 46:707-711, 1970

139. Howell RR, Stevenson RE: The offspring of phenylketonuric women. Soc Biol 18:519-529, 1970

140. Arthur LJ, Hulme JD: Intelligent, small for dates baby born to oligophrenic phenylketonuric mother after low phenylalanine diet during pregnancy. Pediatrics 46:235-239, 1970

141. Farquhar JW, Miller MC, Lindsay G: Maternal phenylketonuria. Br Med J 1:46-47, 1971

142. Brown ES, Waisman HA: Mental retardation in four offspring of a hyperphenylalaninemic mother. Pediatrics 48:401-410, 1971

143. Bourcharlat J, Ledru J, Ratel M, et al: A propos de deux noveaux cas de'enfants microcephales avec retard de croissance intra-uterin nes de mere phenylcetonurique. Ann Med Psychol (Paris) 2:542-550, 1972

144. Scheibenreiter S: Kinder einer phenylketonurischen Frau: Prenatale Phenylalaninvergiftung. Monatsschr Kinderheilk 120: 189-192, 1972

145. Goldstein AD, Auerbach VH, Grover WD: Normal development in an infant of a mother with phenylketonuria. J Pediatr 82:489-491, 1973

146. Perry TL, Hansen S, Tischler B, et al: Unrecognized adult phenylketonuria. N Engl J Med 289:395-398 1973

147. Angeli E, Denman AR, Harris RF, et al: Maternal phenylketonuria: A family with seven mentally retarded siblings. Develop Med Child Neurol 16:800-807, 1974

148. Farquhar JW: Baby of a phenylketonuric mother: Inferences drawn from a single case. Arch Dis Child 49:205-208, 1974

149. Bovier-Lapierre M, Sain-Dizier C, Freycon F, et al: Two infants born to a mother with phenylketonuria—Failure of a low phenylalanine diet during the second pregnancy. Pediatrics 29:51-72, 1974

150. Trouche AM, Gigonnet JM, Dorche C, et al: Les enfants nes de mere phenylcetonurique. Pediatrie 29:33, 1974

151. Frisone L: Contribution to the study of phenylketonuria. G Psichiatr Neuropatol 94:638-659, 1966

152. Menkes JH, Aeberhard E: Maternal phenylketonuria: The composition of cerebral lipids in an affected offspring. J Pediatr 74:924-931, 1969

153. Yu JS, O'Halloran MT: Children of mothers with phenylketonuria. Lancet 1:210-212, 1970

154. Huntley CC, Stevenson RE: Maternal phenylketonuria: Course of two pregnancies. Obstet Gynecol 34:694-700, 1969

155. Hyaneck J, Seemanova E, Sadlova I, et al: Hyperphenylalaninemia. Cas Lek Cesk 110:337-341, 1971

156. Gaudier G, Ponte C, Duquennoy G, et al: Retard de croissance intra-uterin avec microcephalie chez trois enfants nes de mere hyperphenylalaminemique. Ann Pediatr 19:269-276, 1972

157. Hyanek J, Hoza J, Dolezal A, et al: (Child of a mother with hyperphenylalaninemia). Cesk Pediatr 27:489-491, 1972

158. MacCready RA, Levy HL: The problem of maternal phenylketonuria. Am J Obstet Gynecol 113:212-228, 1972

159. Richards BW: Case and kindred in mental deficiency. Br J Psychiatr 125:547-552, 1974

160. Nevsimalova S, Hyanek J, Dittrich G, et al: Maternal hyperphenylalaninemia and intrauterine damage to the CNS. Cesk Neurol Neurochir 37:301-307, 1974

161. Podhradska O, Kalab Z, Vesela V, et al: Maternal phenylketonuria. Cesk Pediatr 29:328-329, 1974

162. Pitt D, Gooch J: The problem of maternal phenylketonuria. Aust Paediatr J 10:337-342, 1974

163. Houston CS, Zaleski WA, Zaleski LA: Cranial growth retardation from maternal phenylketonuria. Am J Roentgenol Radium Ther Nucl Med 122:33-37, 1974

164. Peters WH, Lubs H, Machill G, et al: Prenatal brain damage in maternal untreated phenylketonuria. Zentralbl Gynaekol 97: 905-917, 1975

165. Busch RT, Dukes PC: Progeny, pregnancy and phenylketonuria. N Zeal Med J 82:226-229, 1975

166. Griffin RF, Elsas LJ: Classic phenylketonuria: Diagnosis through heterozygote detection. J Pediatr 86:512-517, 1975

167. Hyanek J, Trnka V, Homolka J, et al: Pregnancy hyperphenylalaninemia and its diagnostic importance. Cas Lek Cesk 114:515-518, 1975

168. Bliumina MG: Obstetrical problems of phenylketonuria. Akush Ginekyl (Mosk) 12:54-56, 1976

169. Hornchen H, Stuhlsatz HW, Plagemann L, et al: Children of mothers with phenylketonuria. Dtsch Med Wochenschr 102:308-312, 1977

170. Blehova B, Finkova A, Pazoutova N: Mother with hyperphenylalaninemia and development of the fetus during a diet in pregnancy. Cesk Gynekol 42:453-454, 1977

171. Nevsinalova S, Hyanek J, Kapras J, et al: Maternal hyperphenylalaninemia and intrauterine damage of the CNS. Magyar Pediater, Supplementum, 9:15, 1975

172. Bessman SP: Genetic mental retardation: A fetal deficiency syndrome—Discussion. Am J Dis Child 113:27-30, 1967

173. Bessman SP: Genetic failure of fetal amino acid "justification": A common basis for many forms of metabolic, nutritional and "non-specific" mental retardation. J Pediatr 81:834-842, 1972

174. Ford RC, Berman JL: Phenylalanine metabolism and intellectual functioning among carriers of phenylketonuria and hyperphenylalaninemia. Lancet 1:767-771, 1977

175. Heterozygote advantage and disadvantage (Editorial). Lancet 1:786, 1977

176. Bessman SP, Williamson ML, Koch R: Diet, genetics, and mental retardation interaction between phenylketonuric heterozygous mother and fetus to produce nonspecific diminution of IQ. Acad Sci 75:1562-1566, 1978

177. Blaskovics ME, Schaeffler CE, Hack S: Phenylalaninemia: Differential diagnosis. Arch Dis Childhood 49:835-843, 1974

178. Gold RJM, Maag UR, Neal JL, et al: The use of biochemical data in screening for mutant alleles and in genetic counselling. Ann Hum Genet 37:315-326, 1974

179. Heterozygote detection during pregnancy. Am J Hum Genet 25:646-654, 1973

180. Kang ES, Kaufman S, Gerald PS: Clinical and biochemical observations of patients with atypical phenylketonuria. Pediatrics 45:83-92, 1970

181. Cowi VA: Changes in heterozygotes for PKU and their possible relation to the environment in utero. J Irish Med Assn 69: 401-404, 1976

182. Marden PM, Smith DW, McDonald MJ: Congenital anomalies in the newborn infant, including minor variations—A study of 4,412 babies by surface examination for anomalies and buccal smear for sex chromatin. J Pediatr 64:357-371, 1964

183. Johnson CF, Peterson RM, Koch R, et al: Congenital and neurological abnormalities in infants with phenylketonuria. Am J Ment Defic 82:376-379, 1978

184. Partington MW: The early symptoms of phenylketonuria. Pediatrics 27:465-473, 1961

185. Phenylketonuria—The present state (Editorial Comment). Med J Aust 1:645 1976

186. Fisch RO, Horrobin JM: Down's syndrome with phenylketonuria. Clin Pediatr 7:226-227, 1968

187. Blehová B, Pazoutová N, Subrt I: Phenylketonuria associated with Down's syndrome. J Ment Defic Res 14:274-275, 1970

188. Benirschke K, Brownhill L, Efron ML, et al: Phenylketonuria associated with Klinefelter's syndrome. J Ment Defic Res 6:44-55 1962

189. Blehová B, Zidlieky A, Pazoutová N, et al: Phenylketonuria in Czechoslovakia. Proc 2nd Congress of International Association of Sciences—Study of Mental Deficiency, Warsaw, Poland, Aug 25-Sep 2, 1970, p 207

190. Blehová B, Pazoutová N, Rakosniková M, et al: Klinika fenylketonurie. Cas Lek Cesk 111:170-172, 1972

191. Drummond JN, Michael AF, Good RA: Tryptophan metabolism in a patient with phenylketonuria and scleroderma. Canad Med Assoc J 94:834-838, 1966

192. Kornreich HK, Shaw KNF, Koch R, et al: Phenylketonuria and scleroderma. J Pediatr 73:571-575, 1968

193. Penrose LS: Peripheral nerve tumors in a case of phenylketonuria. Lancet 1:572-573, 1939

194. Blaskovics ME, Shaw KNF: Hypophosphatasia with phenylketonuria. Z Kinderheilk 117:265-273, 1974

195. Plochl E, Thalhammer O, Weissenbacher G: Foudroyan verlaufende hirnschadigung bei einem saugling mit hyperphenylalaninamie und hypercalcemie. Helv Paediatr Acta 23:292-304, 1968

196. Shaw KNF, Lieberman E, Koch R, et al: Cystathioninuria. Am J Dis Child 113:119-128, 1967

197. Coats S, Norman AP, Woolf LI: Phenylketonuria with normal intelligence and Grower's muscular dystrophy. Arch Dis Child 32:313-317, 1957

198. Roch KS, Cohn RM, Berman P, et al: Phenylketonuria and duchene muscular distrophy—A case report. J Pediatr 88:689-705, 1976

199. Vulovic D: *In* Cohen BE, Rubin MI, Szeinberg A (Eds): Proceedings of the International Symposium on Phenylketonuria and Allied Disorders, Tel-Aviv, June 12-22, 1969. Tel-Aviv, 1971, p 237

200. Crome L: The association of phenylketonuria with leucodystrophy. J Neurol Neurosurg Psychiatry 25:149, 1962

201. Richards BW, Sylvester PE, Hodgson SJ: Familial occurrence of juvenile amaurotic family idiocy and phenylketonuria in the same subjects. J Ment Defic Res 9:210-218, 1965

202. Smith AJ, Strang LB: An inborn error of metabolism with the urinary excretion of alpha-hydroxybutyric acid and phenylpyruvic avid. Arch Dis Child 33:109-113, 1958

203. Fishler K: Psychological aspects of phenylketonuria, *In* Bickel H, Hudson FP, Woolf LI (Eds): Phenylketonuria and Some Other Inborn Errors of Amino Acid Metabolism. Stuttgart, Georg Thieme Verlag, 1971, pp 213-219

204. Pueschel SM, Yeatman S: An educational and counseling program for phenylketonuric adolescent girls and their parents. So Work Health Care 3:29-36, 1977

205. Acosta PB, Wenz E: Nutrition in phenylketonuria, *In* Bickel H, Hudson FP, Woolf LI (Eds): Phenylketonuria and Some Other Inborn Errors of Amino Acid Metabolism. Stuttgart, Georg Thieme Verlag, 1971, pp 181-196

206. Committee on Genetics. Screening for congenital metabolic disorders in the newborn infant: Congenital deficiency of thyroid hormone and hyperphenylalaninemia. Pediatrics 60:389-404, 1977

207. Lutz P: Clinical biochemistry and pathogenesis, *In* Bickel H, Hudson FP, Woolf LI (Eds): Phenylketonuria and Some Other Inborn Errors of Amino Acid Metabolism. Stuttgart, Georg Thieme Verlag, 1971, pp 56-64

208. Grumer HD, Koblet H, Woodard C: Phenylalanine metabolism in the phenylketonuric conditions—I. Distribution, pool size and turnover rate in human phenylketonuria. J Clin Invest 40: 1758-1765, 1961

209. Anderson EV, Siegel FS: Behavioral and biochemical correlates of diet change in phenylketonuria. Pediatr Res 10:10-17, 1976

210. Thalhammer O, Havelec L, Knoll E, et al: Intellectual level (IQ) in heterozygotes for phenylketonuria (PKU)—Is the PKU gene also acting by means other than phenylalanine-blood level elevation. Hum Genet 38:285-288, 1977

211. Magalini SI, Bondoli A, Ranieri R, et al: Comparison of CSF-free amino acid concentrations among various neuropathological conditions. Critical Care 4:153-156, 1976

212. McKean CM: The effects of high phenylalanine concentrations on serotonin and catecholamine metabolism in the human brain. Brain Res 47:469-476, 1972

213. Linderkamp O, Schaub J, Riegel KP: Hypervolaemia in phenylketonuria. Lancet 2:772, 1977

214. Ziyai F, Wong PWK, Justice P, et al: Protein-induced hypoglycemia in a phenylketonuric patient. J Pediatr 92:681-682, 1978

215. Brady RO: Inherited metabolic diseases of the nervous system. Science 193:733-739, 1976

216. Fisch RO, Bilek MK, Bruhl HH: Causes of death of institutionalized phenylketonuric (PKU) patients—A national survey. Minn Med 306-309, 1976

217. Crom L: The morbid anatomy of phenylketonuria, *In* Bickel H, Hudson FP, Woolf LI (Eds): Phenylketonuria and Some Other Inborn Errors of Amino Acid Metabolism. Stuttgart, Georg Thieme Verlag, 1971, pp 126-131

218. Jervis GA: Phenylpyruvic oligophrenia: An introductory study of fifty cases of mental deficiency associated with excretion of phenylpyruvic acid. Arch Neurol Psychiat 38:944-963, 1937

219. Hudson FP, Mordaunt VL, Leahy I: Evaluation of treatment begun in the first months of life in 184 cases of phenylketonuria. Arch Dis Childhood 45:5-12, 1970

220. Agrawal HC, Bone AH, Davidson AN: Inhibition of brain protein synthesis by phenylalanine. Biochem J 112:27, 1969

221. Chrome L, Tymms V, Woolf LI: A chemical investigation of the defects of myelination in phenylketonuria. J Neurol Neurosurg Psychiat 25:143-148, 1962

222. Williamson M, Koch R, Bessman SP, et al: The relating between heterozygosity and IQ in phenylketonuria—Am Pediat Soc, 86 Annual Meeting: Abstract 432. Pediat Res 10:373, 1976

223. Brandt IK: PKU and hypothyroidism blood test for newborn infants. J Indiana State Med Assn 71:329, 1978

Specialty Conference

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Hypoparathyroidism

WILLIAM L. NYHAN, MD, PHD:* *This conference has been designed to examine the variety of presentations of hypoparathyroidism. Dr. Jones will begin with a discussion of the physiology of parathyroid hormone* (PTH) *and the pathophysiology of hypoparathyroidism, as well as the clinical features, diagnosis and therapy.*

KENNETH LEE JONES, MD:† We shall discuss specific aspects of presentation, diagnosis and therapy, as well as reviewing three cases. A few comments on the physiology of parathyroid hormone (PTH) are necessary. Parathyroid hormone has a molecular weight of approximately 9,500. It is secreted following the cleavage of a larger prohormone whose molecular weight is 11,000 to 12,000. Upon release, PTH is rapidly cleaved into smaller fragments. Although biologically inactive, these fragments are immunologically active, thereby complicating the radioimmunoassy (RIA) of parathyroid hormone. Nevertheless, the ability of investigators to measure parathyroid hormone accurately by RIA has led to considerable advancement in our knowledge of the physiology of PTH.

The actions of parathyroid hormone are given in Table 1. In the kidney, its primary actions are to decrease the tubular reabsorption of phosphate, leading to phosphaturia and, concomitantly, to increase the tubular reabsorption of calcium. In bone, PTH increases the release of calcium and promotes bone remodeling. In the intestine, PTH enhances the absorption of calcium, largely through its effect on the metabolism of vitamin D. Problems in distinguishing between primary and secondary actions of PTH complicate our understanding of this area of physiology. The absorption of calcium from the gut is an example. Results of recent investigations have shown that PTH increases l-α-hydroxylation of vitamin D in the kidney to form 1,25 dihydroxyvitamin D, the most active form of this vitamin. Therefore, it appears that enhancement of calcium absorption is not a primary effect of PTH but, rather, is secondary to promotion of increased production of 1,25 dihydroxyvitamin D. It is helpful, in view of the complicated interactions in calcium-phosphorus metabolism, to remember that the major function of PTH is to maintain serum levels of calcium within the normal range.

The pathophysiology of hypoparathyroidism follows logically from an understanding of the actions of PTH. If there is inadequate circulating parathyroid hormone, renal excretion of phosphorus and absorption of calcium from the kidney, bone and gut do not proceed efficiently. Therefore, the concentration of calcium in the serum falls and that of phosphorus rises. In pa-

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ABBREVIATIONS USED IN TEXT

DHT = dihydrotachysterol
PTH = parathyroid hormone
RIA = radioimmunoassay

TABLE 1.—*Actions of Parathyroid Hormone*

Kidney
Increases tubular reabsorption of calcium
Decreases tubular reabsorption of phosphorus
Bone
Increases release of calcium
Promotes remodeling of bone
Intestine
Enhances absorption of calcium

tients with hypocalcemia and hyperphosphatemia there are a number of diagnostic possibilities. The availability of a radioimmunoassay for PTH facilitates diagnosis, permitting the classification of hypoparathyroidism into two major categories: one in which the levels of PTH are low and another in which they are elevated.[1] Low levels of PTH may result from an abnormality either in the reception of a feedback signal by the cells that secrete PTH or in the ability of these cells to respond. Failure to respond may be due to transient suppression of the cells or may result from more permanent problems including failure of the parathyroid glands to develop or their surgical removal or destruction due to disease. The three cases discussed later illustrate conditions in which circulating levels of PTH are low.

In hypoparathyroid states associated with elevated levels of PTH that can be radioimmunoassayed, the pathophysiology is not completely clear; but, presumably, one or more of the following mechanisms is operative: (1) abnormal conversion of the hormone to an inactive form, (2) lack of a cofactor necessary for the functioning of the hormone, (3) presence of an inhibitor of hormone action, (4) defect in the receptor or second messenger system in one or more of the target cells, (5) defect in the cellular response to the second messenger system or (6) lack of substrate for the target cells.

Specific examples of hypoparathyroidism in which PTH is deficient are listed in Table 2. One category of hypoparathyroidism results from absence of the parathyroid glands, or their damage or insufficiency. Surgical procedures on the thyroid or the parathyroid glands (case 2) may be

TABLE 2.—*Hypoparathyroid States in Which Parathyroid Hormone is Deficient*

Hypoparathyroidism secondary to absence or damage of parathyroid glands
Following surgical procedures
Thyroid
Parathyroid
Radical neck
Radioiodine
Drug related
l-Asparaginase
Damage in hemochromatosis
Damage by metastatic tumor
Branchial dysembryogenesis
DiGeorge syndrome
Other branchial arch abnormalities
Familial
Sex linked
Undetermined mode of transmission
Idiopathic or sporadic (presumably autoimmune)
Isolated deficiency of PTH
Deficiency of PTH with other endocrine deficiencies
Inadequate PTH synthesis in neonates
Hypoparathyroidism secondary to suppression of parathyroid function
Neonatal secondary to maternal hypercalcemia
Secondary to hypercalcemia
Post resection of parathyroid adenoma, hyperplasia
Secondary to nonparathyroid hypercalcemia
Deficiency of magnesium

PTH = parathyroid hormone

followed by hypoparathyroidism. Postirradiation damage is a rare cause of hypoparathyroidism in children. There have been a few case reports in which patients had been treated with iodine 131 for hyperthyroidism and subsequently hypoparathyroidism has developed. Hemochromatosis and metastatic malignant replacement of the parathyroid glands occur rarely in children.

Branchial dysembryogenesis is a more common cause of hypoparathyroidism in children. Perhaps the best known example is the DiGeorge syndrome in which the thymus as well as the parathyroids fail to develop. In this situation, hypoparathyroidism is associated with an immunodeficiency disease, and may be accompanied by facial abnormalities and congenital heart disease. The association of hypoparathyroidism with other abnormalities of branchial arch development has been recently reexamined. In approximately 150 patients with hypoparathyroidism,[2] very few had the DiGeorge syndrome, but many had developmental abnormalities such as cleft palate. Familial hypoparathyroidism has been reported. In some, a sex-linked mode of inheritance has been estab-

lished. The form of hypoparathyroidism we most commonly see is also called sporadic, autoimmune or idiopathic hypoparathyroidism.

The second major category of hypoparathyroidism (Table 2) includes conditions in which there is suppression of PTH secretion. We see this in newborn infants whose parathyroid glands have been suppressed by maternal hypercalcemia, or in those in whom there is a condition involving apparent immaturity of the neonatal parathyroid glands. The disease becomes symptomatic in the infants receiving large amounts of phosphorus contained in cow's milk formulas which depress the serum concentration of calcium and, in turn, prevent adequate secretion of PTH. PTH secretion may also be defective in those with magnesium deficiency.

The primary clinical features of hypoparathyroidism are similar to those of hypocalcemia. They vary with the age of each patient and the severity of the depression of the serum concentration of calcium. Table 3 summarizes the signs and symptoms of hypoparathyroidism as they involve three systems—the neuromuscular, ectodermal and ocular. Neuromuscular irritability is the most common manifestation and may present as classic tetany. Muscle cramps and paresthesias are common, more often recognized in older persons who are able to describe their symptoms. Hoarseness may result from laryngospasm, as occurred in one of our patients. Carpopedal spasm may become evident or be accentuated by hyperventilation. The Chvostek and Trousseau signs, and the peroneal reflex are all signs which may be seen on physical examination. Signs of increased intracranial pressures are often seen; papilledema may be present although it is not always associated with increased intracranial pressure. Convulsions are frequently presenting signs and though usually generalized, they may be focal. Metastatic calcification may develop and frequently involves the basal ganglia. Cataracts also frequently occur. Ectodermal complaints include loss of hair, delayed eruption or premature loss of teeth, enamel hypoplasia and severe dental caries. Mucocutaneous monilial infections are common and persistent. The skin may be dry and scaly; rarely, an exfoliative dermatitis develops. Transverse ridging of the nails may occur.

The primary laboratory findings for hypoparathyroidism are hypocalcemia and hyperphosphatemia. In the presence of these conditions, one can rule out only renal glomerular insufficiency, as there is little else in the differential diagnosis. The next task is to establish whether hypoparathyroidism is due to a deficiency of PTH.

The major goal of therapy is to maintain the serum concentration of calcium in the normal range. Establishing normocalcemia will correct many of the symptoms and signs of hypoparathyroidism, especially the neuromuscular manifestations. Of course, hypoplasia of dental enamel, cataracts, and the chronic moniliasis seen in approximately 20 percent of patients will not resolve.

The treatment of chronic hypoparathyroidism should be matched with the severity of the illness.[4] In mild transient hypoparathyroidism which may follow surgical removal of parathyroid tissue[5] or which occurs in newborn infants, calcium supplementation may be all that is required. In more severe and chronic hypoparathyroidism, seen in

TABLE 3.—*Signs and Symptoms of Hypoparathyroidism*

Symptoms	Signs
Neuromuscular	
Tetany	Carpopedal spasm—increased with hyperventilation
Convulsions	Chvostek sign
Muscle cramps	Trousseau sign
Paresthesias	Peroneal sign
Hoarseness secondary to laryngospasm	Hyperreflexia
	Increased intracranial pressure
Ocular	
Cataracts	Papilledema
Ectodermal	
Hair loss	Dry scaly skin
Delayed dental eruption	Brittle, dull hair; alopecia
Premature loss of teeth	Transverse ridging of nails
Mucocutaneous candidiasis	Hypoplasia of dental enamel
	Severe dental caries

patients following total removal of the parathyroid glands as well as in most patients with idiopathic hypoparathyroidism, therapy with vitamin D is required. It may be used either alone or with calcium supplementation. I prefer to use dihydrotachysterol (DHT) when vitamin D therapy is indicated. This drug has a more rapid onset and probably a better phosphaturic effect than other available preparations. In addition, DHT is inactivated more rapidly so that, if hypervitaminosis D and hypercalcemia develop, discontinuation of therapy results in a more rapid resolution. Furthermore, DHT does not have the propensity to accumulate in fatty tissues that other vitamin D preparations have.

The plan of vitamin D therapy should be dictated by the severity of symptoms. In a patient with pronounced symptoms of hypocalcemia, it is useful to give a loading dose. In treating infants, we use 1 mg of DHT a day for four days and then decrease the dose (1 mg is approximately equivalent to 120,000 units of vitamin D). In severely ill older children we begin with 2.5 mg per day for four days before beginning to decrease the dose. In most patients symptoms are not severe and we can begin with much lower doses, starting with 0.125 to 0.2 mg of DHT, increasing the dose every week or two until serum calcium levels approach the normal range.

DR. NYHAN: *Dr. Murphy will present case 1.*

JAMES MURPHY, MD:* A male infant weighing 2,693 grams was born to a 28-year-old mother after a 41-week gestation. The pregnancy was complicated by renal calculi, which required surgical removal at six months, and by pyelonephritis, treated with sulfanilamide at 36 weeks of gestation. In retrospect, the mother also experienced polyuria, polydipsia, nervousness and constipation throughout the pregnancy. In addition, the mother had a history of asthma, for which she was receiving Marax (ephedrine sulfate, theophylline and hydroxyzine hydrochloride), hydroxyzine pamoate (Vistaril) and beclomethasone dipropionate. The delivery was uneventful. The infant was breast-fed for two days and then given a prepared formula after mastitis developed in the mother. Several formulas were tried because the child had symptoms of colic, but the symptoms did not resolve with the changes in formula. On the tenth day after delivery when diarrhea developed, the infant had several episodes of vomiting and a left-sided major motor seizure involving the face, arm and leg. He was admitted to a local hospital.

On admission, the baby was lethargic. Serum levels of calcium and magnesium were 6.1 and 1.0 mg per dl, respectively. Values for blood urea nitrogen (BUN), electrolytes, glucose and creatinine were within normal limits. The leukocyte count was 27,400 per cu mm with a normal differential and the hematocrit was 56 percent. Cerebrospinal fluid concentrations of glucose and protein were normal. All cultures were negative and x-ray films of the long bones and skull showed no abnormalities.

The infant was given calcium intravenously and supplemental calcium was given orally. In addition, he was fed a formula in which the ratio of calcium to phosphorus was 2:1. On the day following admission his serum concentrations of calcium and phosphorus were each 7.9 mg per dl. A repeat measurement of the magnesium level was 1.5 mg per dl and the total serum protein was 4 mg per dl. On day six, administration of vitamin D was begun. The infant's PTH was 50 pg per ml (normal 275 to 675 pg per ml), exceptionally low in view of the patient's low serum concentration of calcium. The infant's mother was found to have a serum concentration of calcium of 11.4 mg per dl and a phosphorus level of 3.0 mg per dl. We made a diagnosis of neonatal hypoparathyroidism secondary to maternal hyperparathyroidism.

DR. JONES: This infant presented with classic neonatal tetany. In patients with this disorder, symptoms develop in the first two weeks of life. Symptoms followed a feeding change from breast milk, which has a calcium/phosphorus ratio of 2:1, to a formula which has a calcium/phosphorus ratio of about 1:1. Furthermore, the concentration of phosphorus in the formula is three times greater than that in breast milk. Symptoms of hypocalcemia with jitteriness, colic and seizure developed in the infant. The laboratory confirmed the presence of hypocalcemia and hyperphosphatemia.

There are several differential diagnostic considerations. The most common condition seen at this age is that of transient hypoparathyroidism of the newborn. With current feeding regimens, this syndrome is seen less frequently, although it

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still occurs in premature infants following obstetrical complications, and in infants of diabetic mothers. In the past it was also seen in term infants who were given whole milk or evaporated milk formulas, both having phosphate contents about 6½ times greater than that of breast milk. Another diagnostic possibility was the DiGeorge syndrome. The absence of facial abnormalities, cardiovascular abnormalities and immunodeficiency, and the presence of the thymus ruled out this diagnosis. This infant may also have had congenital absence or hypoplasia of the parathyroid glands, or one of the varieties of familial hypoparathyroidism. The diagnosis in this patient was dependent on the diagnosis of hyperparathyroidism in his mother.[6] The mother had emotional difficulties, renal stones, polyuria, recurrent urinary tract infections and constipation. The serum concentrations of calcium and PTH were elevated.

To distinguish permanent forms of hypoparathyroidism from transient forms[7] such as that associated with maternal hyperparathyroidism,[8] one must decrease the therapy and follow the patient closely for recurrence of hypocalcemia. This task is easier if it has not been necessary to use vitamin D. While waiting for an infant's suppressed parathyroid glands to begin functioning appropriately we increase the dietary calcium supplement to achieve a calcium/phosphorus ratio of 4:1. In this infant an intake of 720 ml of formula per day in combination with the calcium supplement produced a calcium/phosphorus ratio of 3:1. He was also treated with vitamin D and aluminum hydroxide and his serum concentrations of calcium and phosphorus were corrected. When therapy was withdrawn, it was discontinued in reverse order: the phosphate complexing agents first, vitamin D second and calcium supplementation last.

DR. NYHAN: *Dr. Murphy will present case 2 which illustrates a different problem.*

DR. MURPHY: A 15-year-old boy was healthy until the age of 8 years, when he noted the onset of abdominal pain, vomiting and dysuria. Analysis of the urine showed pyuria. He was treated with antibiotics, but urine cultures were negative. The symptoms recurred four months later and findings of a urine analysis at that time showed hematuria and pyuria, and the boy was treated with a sulfonamide. Cultures of the urine were again negative. An intravenous pyelogram and voiding cystourethrogram were normal. Serum levels of calcium and phosphorus were also normal. Three months later, after recurrent urinary tract symptoms, a urine culture yielded greater than 100,000 Escherichia coli, but multiple repeat cultures in the absence of therapy showed no bacterial growth. Findings of a roentgenogram of the abdomen showed a density in the left kidney. A 24-hour urine specimen showed normal calcium but low phosphate excretion. Hematuria and pyuria were documented intermittently. Nine serial measurements of the serum concentrations of calcium and phosphorus were obtained. Five determinations of calcium were in the range of 12 to 13 mg per dl and the phosphorus values were in the range of 2.5 to 3.0 mg per dl. Polyuria, polydipsia and worsening of abdominal pain developed. X-ray films showed a urethral stone which was subsequently surgically removed. A diagnosis of hyperparathyroidism was made. When the surgical procedure was done, no adenoma was clearly identified but 2½ parathyroid glands were removed. Pathologic evaluation showed an adenoma in the parathyroid gland from the left upper pole of the thyroid. The remainder of the glandular tissue was normal. Hypocalcemia developed in the patient postoperatively, and treatment was begun with calcium and vitamin D.

Four years following surgical operation, the patient appeared to require gradually increasing amounts of vitamin D and, eventually, a dosage in excess of 300,000 units per day was prescribed. Noncompliance was suspected. Subsequently, the patient became intoxicated with vitamin D, presumably as a result of beginning to take all of the medications which were being prescribed. His medications were discontinued and his serum level of calcium returned to normal and then became slightly low. On reinstitution of calcium supplementation and DHT normal serum concentrations of calcium and phosphorus were maintained.

DR. JONES: Two interesting points are illustrated by this boy's course. The first is relevant to hyperparathyroidism and its surgical treatment, and the second to the development of hypercalcemia secondary to excessive vitamin D therapy. Hyperparathyroidism is an unusual condition in children. Only 36 cases had been reported up to 1970.[9] Manifestations include urinary tract infections, polyuria, polydipsia, hematuria and other symptoms associated with calculi. The ther-

apy of hyperparathyroidism is surgical. In the literature the incidence of permanent hypoparathyroidism secondary to parathyroid excision for the removal of adenomata or hyperplastic glands should be 1 percent to 2 percent, or less. When adenomas are present, either singly or multiply, they should be removed. When parathyroid hyperplasia is found, the approach is to reduce the number of glands to 1½ or 2, leaving approximately 150 mg of tissue. In this patient there was difficulty identifying the adenomatous gland. I think that if the surgeon had been able to identify the adenoma, he would have removed it without doing a more extensive surgical procedure. The surgeon apparently removed too much tissue (particularly in view of the fact that the other three glands were suppressed) which resulted in permanent hypoparathyroidism. Therapy was a problem, probably because of noncompliance. One of the factors that may have led to this boy's poor compliance was the large number of medications he was required to take. When he came to San Diego he was receiving 1.75 mg of DHT, which amounted to 15 tablets (0.125 mg per tablet) and provided the equivalent of 210,000 units of vitamin D. In most patients satisfactory control can be achieved with between 80,000 and 120,000 units per day. The patient was also receiving calcium supplementation in the form of a combination medication which contained calcium and 2,500 units of vitamin D per tablet and, in addition, 150,000 units of vitamin D_2. The total exceeded 360,000 units of vitamin D per day. It is not surprising that, with improved compliance, hypercalcemia developed. Following admittance to hospital for hypervitaminosis D, the patient was given 0.4 mg of DHT. The dose has been increased gradually to 0.8 mg of DHT (about 100,000 units of vitamin D) and he is doing well. The most recent test showed a serum calcium level of 10.1 mg per dl, which is much higher than we seek in the management of hypoparathyroidism. In the presence of PTH deficiency there is decreased reabsorption of calcium in the kidney and increased urinary excretion of calcium.[4] Therefore, we aim to keep serum values lower to prevent nephrocalcinosis.

DR. NYHAN: *Dr. Murphy will now present case 3.*

DR. MURPHY: A 13-year-old boy was noted to have a decrease in the rate of linear growth, although he continued to gain weight. He was found to have dry, scaly skin and to be lethargic. The thyroxine (T4) level was 2.3 μg per dl and the serum concentration of calcium was 8.1 mg per dl. Treatment was begun with administration of 0.2 mg of L-thyroxine per day and there was improvement in the boy's lethargy and dry skin. He also began to lose weight.

The patient's condition was evaluated at Camp Pendleton Naval Hospital after discontinuing thyroid replacement for three weeks. T4 was 2.6 μg per dl and the triiodothyronine (T3) resin uptake was 32 percent. There were positive antithyroid antibodies. A diagnosis of Hashimoto thyroiditis was made. The boy's bone development was normal for his age. He had mild papilledema, but no other evidence of increased intracranial pressure. Visual fields were normal, and there was no enlargement of his blind spot. Computerized axial tomography (CAT) of the skull and brain scan showed no abnormalities. He was discharged from hospital on a regimen of 0.15 mg of L-thyroxine per day.

He did well for a year but then had a generalized seizure without fever which lasted four to five minutes. Administration of phenobarbital was begun. The boy had had a history of several febrile seizures as a child and had received phenobarbital between the ages of 5 and 7. He said he had not had headaches, nausea, vomiting, muscle twitches, cramps, blurred vision or diarrhea. There was a history of recurrent pneumonia between the ages of 1 and 5, requiring 40 admissions to hospital. There was no family history of endocrine disease. Findings of a physical examination on admission to the Naval Regional Medical Center showed that the boy's height was at the 3rd percentile and his weight at the 84th percentile. Other results of the physical examination were normal, except for dry, scaly skin and slightly blurred optic disks. There was no palpable thyroid and reflexes were hypoactive. Laboratory findings showed serum levels of calcium and phosphorus of 7.4 and 7.5 mg per dl, respectively. The level of PTH was 156 pg per ml. An electroencephalographic study displayed epileptiform discharges in the frontal regions. A diagnosis of hypothyroidism and hypoparathyroidism was made.

DR. JONES: Another chapter has been added to this patient's story. His physician recently informed me that polyuria and polydipsia had developed. The blood glucose level was 625 mg per

dl. Therefore, diabetes mellitus has been added to his spectrum of endocrine hypofunction.[10]

There are several interesting points about this case: one is that there are three disorders of endocrine function. The treatment of the hypothyroidism may be relevant to the development of symptomatic hypocalcemia. Thyroid hormone decreases the absorption of calcium from the gut, and we often find mild hypocalcemia in patients who have hyperthyroidism and normal parathyroid function. The thyroxine therapy may have precipitated the symptoms and worsened the laboratory manifestations of his hypoparathyroidism. States of endocrine hypofunction which are associated with hypoparathyroidism include Hashimoto thyroiditis and diabetes mellitus, which are the two conditions seen most commonly in the pediatric age range. In adults, pernicious anemia and ovarian failure are being reported with increasing frequency. Addison disease is a particular problem because, in initiating therapy with cortisol, we add another antagonist to the action of PTH, decrease calcium absorption and often alter the effective dose of vitamin D.[11]

QUESTION FROM THE AUDIENCE: What is the polyuria due to?

DR. JONES: In hyperparathyroidism, it is due to hypercalciuria. The urinary Sulkowitch reaction, which measures calcium excretion in the urine, may be a helpful procedure in the follow-up of patients receiving treatment with vitamin D, although the serum level of calcium remains the best measure and must be followed as well. PTH increases renal calcium reabsorption, while vitamin D increases the absorption of calcium from the gut and also the mobilization of calcium from bone. In a patient who has no parathyroid hormone and who is treated with administration of vitamin D, normocalcemia is often achieved at the expense of calciuria developing. It is most advisable to keep such a patient's calcium level in the low normal (8.5 to 9 mg per dl) or even slightly low (8 to 8.5 mg per dl) range. When there are higher serum levels of calcium in such patients, excretion of calcium in the urine increases and nephrolithiasis or nephrocalcinosis (or both) may occur.

QUESTION FROM THE AUDIENCE: Does neonatal hypoparathyroidism associated with maternal hyperparathyroidism appear to result from suppression of parathyroid hormone or calcium in the mother?

DR. JONES: Most polypeptide hormones cross the placenta very poorly. The severity of depression of the neonatal parathyroid glands seems to correlate with maternal hypercalcemia.

In summary, we have reviewed the physiology of parathyroid hormone and the pathophysiology of hypoparathyroidism including clinical signs and symptoms as well as possible causes. Case reports for three patients have been presented to illustrate the problems that may occur in such clinical situations.

REFERENCES

1. Nusynowitz ML, Frame B, Kolb FO: The spectrum of the hypoparathyroid states: A classification based on physiologic principles. Medicine 55:105-119, Mar 1976
2. Miller MJ, Frame B, Poznanski AK: Branchial anomalies in idiopathic hypoparathyroidism: Branchial dysembryogenesis. Henry Ford Hospital Med J 20:3-14, 1972
3. Peden VH: True idiopathic hypoparathyroidism as a sex-linked recessive trait. Am J Hum Genet 12:323-337, Sep 1960
4. Avioli LV: The therapeutic approach to hypoparathyroidism. Am J Med 57:34-42, Jul 1974
5. Wade JSH, Goodall P, Deane L, et al: The course of partial parathyroid insufficiency after thyroidectomy. Br J Surg 52:497-503, Jul 1965
6. Hartenstein H, Gardner LI: Tetany of the newborn associated with maternal parathyroid adenoma. N Engl J Med 274:266-268, Feb 1966
7. Rosenbloom AL: Transient congenital idiopathic hypoparathyroidism. South Med J 66:667-670, Jun 1973
8. Wagner G, Transbol I, Melchior JC: Hyperparathyroidism and pregnancy. Acta Endocr 47:549-564, Dec 1964
9. Bjernulf A, Hall K, Sjogren L, et al: Primary hyperparathyroidism in children: Brief review of the literature and a case report. Acta Paediatr Scand 59:249-258, May 1970
10. Blizzard RM, Chee D, Davis W, et al: The incidence of parathyroid and other antibodies in the sera of patients with idiopathic hypoparathyroidism. Clin Exp Immunol 1:119-128, Apr 1966
11. Lukert BP, Adams JS: Vitamin D metabolism in man: Effect of corticosteroids. Arch Intern Med 136:1241-1248, Nov 1976

Refer to: Jacobs MD: Vitamin D deficient states—Pathophysiology and treatment—Medical Staff Conference, University of California, San Francisco. West J Med 131:305-312, Oct 1979

Vitamin D Deficient States

Pathophysiology and Treatment

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, CA 94143.

DR. SMITH:* *At Moffitt Hospital, it has been traditional at the end of the academic year for us to ask the Chief Medical Residents to present Medical Grand Rounds. This permits us to express publicly our deep appreciation for the remarkable leadership they have brought to our patient care and learning programs. Dr. Mark D. Jacobs will discuss the topic of vitamin D deficient states.*

DR. JACOBS:† Over the last decade, there have been exciting advances in our understanding of vitamin D metabolism. Rather than a vitamin, which functions as a coenzyme biochemically, vitamin D is a steroid hormone, more accurately a prohormone, which undergoes a series of enzymatic activation steps before influencing mineral homeostasis. Each step is subject to important controls and may be impaired by one or more disease processes. Pathologic processes involving such varied organ systems as the liver, kidneys, parathyroids, gastrointestinal tract, adrenals and ovaries may have profound effects on calcium and bone through abormalities in vitamin D metabolism. As medical advances have permitted longer survival in patients with serious illnesses involving these organs, the importance of diagnosis and treatment of associated bone disease increases. This paper will review the pathophysiology of defects in vitamin D metabolism, viewed as vitamin D *deficient states*, and outline our current understanding of their treatment.

The primary functions of vitamin D are (1) maintenance of normal serum calcium and phosphorus, (2) bone and epiphyseal mineralization and (3) prevention of myopathy.

In order to carry out these functions, vitamin D acts upon intestine, kidney and bone, and cooperates with parathyroid hormone in a complex regulatory system[1] (Figure 1).

Humans have two main sources of vitamin D[2] (Figure 2); the most important is the skin, where 7-dehydrocholesterol undergoes photolysis, upon exposure to the ultraviolet component of sunlight, to form cholecalciferol (D_3). In normal persons, adequate sunlight and sufficient dietary calcium and phosphorus will prevent the development of rickets or osteomalacia. This bone disease is the hallmark of the vitamin D deficient state, and is characterized by an increase in the volume of unmineralized osteoid, resulting in pain, weakness, deformity and fracture.[4] This type of deficiency disease was prevalent during the Industrial Revo-

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†Mark D. Jacobs, MD, Chief Medical Resident at the time of this Grand Rounds. He is now on the faculty of the medical school at Brown University, Providence, Rhode Island.

lution, when air pollution and indoor confinement severely restricted exposure to sunlight.[3]

Today, we can be independent of the sun for vitamin D because of adequate dietary sources. As little as 400 IU per day in growing children, and 100 IU per day in adults, will prevent deficiency. Although D_3 is naturally found in butter, eggs and cod liver oil, our most reliable sources are foods such as bread and milk (400 IU per quart) which are fortified with D_2 (ergocalciferol). This compound is easily manufactured by the ultraviolet irradiation of ergosterol from yeast and fungi. D_2 and D_3 are essentially of equal potency,[2] and from this point the terms are used interchangeably.

Dietary vitamin D mixes with micelles and is absorbed in the proximal small bowel. Bound to a specific transport globulin, it reaches the liver where calciferol-25-hydroxylase converts it to 25-hydroxy vitamin D (25-OH-D_3, calcifediol). This reaction is loosely controlled but seems to be inhibited in states of excess vitamin D stores. 25-OH-D_3 is the major form in the circulation and a large percentage undergoes enterohepatic cycling. The level of 25-OH-D_3 is mainly a function of intake (sunlight and diet) balanced against loss (degradation, enterohepatic losses, proteinuria) and therefore its determination is important in making the diagnosis of deficiency or intoxication.[2]

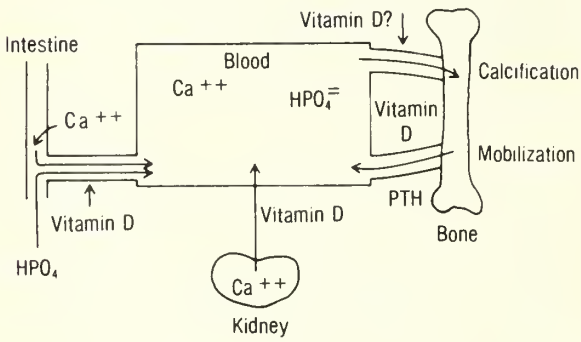

Figure 1.—Sites of vitamin D action (reproduced with permission from DeLuca H and Arch Intern Med[1]).

25-OH-D_3 can be further hydroxylated in the 1,24, or 26 positions. The 1α-hydroxylase enzyme resides exclusively in the renal tubules and is the most important control step in mineral homeostasis. Production of 1,25-$(OH)_2D_3$ from 25-OH-D_3 is tightly controlled by parathyroid hormone (PTH), phosphate and its own levels. 1,25-$(OH)_2D_3$ is the most potent vitamin D metabolite which raises serum calcium and is the only naturally occurring form that, in physiologic amounts, can maintain normal serum calcium despite nephrectomy or parathyroidectomy. In fulfilling the modern concept of hormonal regulatory systems, 1,25-$(OH)_2D_3$ is synthesized exclusively in the kidney, affects target sites in the intestine, bone and kidney, and is under tight regulatory feedback inhibition[5] (Figure 3).

Hypocalcemia causes the parathyroid glands to secrete parathyroid hormone, which stimulates the 1-hydroxylase to synthesize 1,25-$(OH)_2D_3$ and which suppresses the alternate 24-hydroxylase

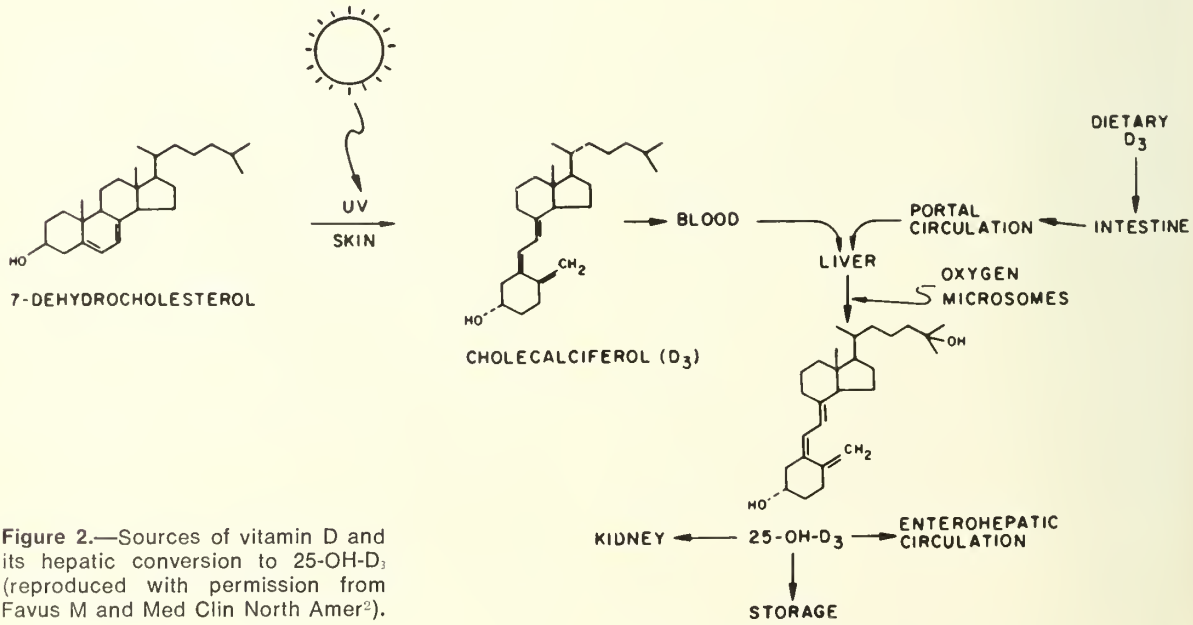

Figure 2.—Sources of vitamin D and its hepatic conversion to 25-OH-D_3 (reproduced with permission from Favus M and Med Clin North Amer[2]).

pathway. 1,25-$(OH)_2D_3$ increases intestinal calcium absorption, and, in concert with PTH, enhances calcium reclamation in the kidney and mobilization of calcium from bone. Extra phosphate that is mobilized is excreted through the inhibitory effect of PTH on tubular phosphate reabsorption. As serum calcium normalizes, PTH falls and 24-hydroxylation of 25-OH-D_3 is stimulated. *Hypophosphatemia* directly stimulates the synthesis of 1,25-$(OH)_2D_3$, which increases intestinal phosphate absorption and, in the absence of PTH, enhances renal phosphate reabsorption.[2]

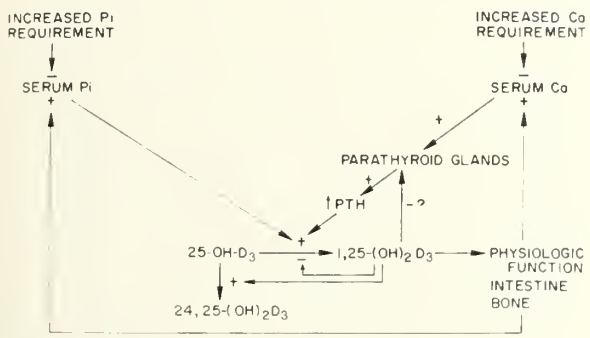

Figure 3.—Regulatory pathway of vitamin D metabolism—maintenance of normal serum calcium and phosphate by feedback control (reproduced with permission from Favus M and Med Clin North Amer[2]).

Steroid Mode of Action

Structurally 1,25-$(OH)_2D_3$ resembles other steroid hormones with its complex ring structure separating key hydroxyl groups. In the intestine, 1,25-$(OH)_2D_3$ enters the intestinal cell and binds to a specific cytosol receptor. This hormone-receptor complex migrates to the nucleus where it interacts with nuclear chromatin, activates the expression of a section of deoxyribonucleic acid (DNA) and directs the synthesis of a new calcium binding protein which is believed to participate in the intestinal uptake of calcium.[2]

Consequences of vitamin D deficiency are (1) osteomalacia due to inadequate concentration of calcium and phosphate at mineralization sites and lack of some direct but as yet undefined effect of vitamin D on bone, (2) hypocalcemia and negative calcium balance secondary to intestinal malabsorption, (3) secondary hyperparathyroidism with hypophosphatemia, (4) proximal muscle weakness which may be secondary to elevated PTH, hypophosphatemia or lack of direct effect of vitamin D. Clinically, osteomalacia[4] is characterized by bone pain, particularly of the spine, ribs, pelvis and upper femurs, which is made worse by effort and direct pressure. Patients may limp or waddle as a result of weakness and

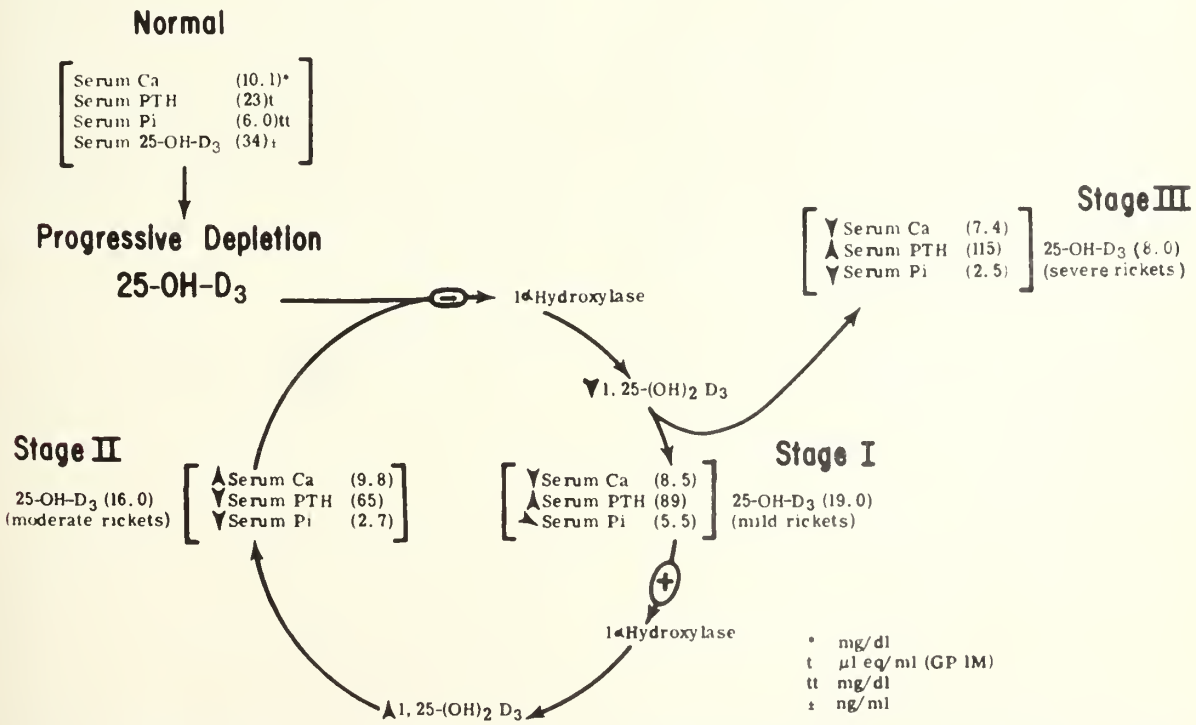

Figure 4.—Stages of vitamin D deficiency—laboratory and bone findings (reproduced with permission from Arnaud S and publisher[7]).

pain. Long-standing deficiency causes such bone undermineralization and softening that skeletal deformities result. Associated laboratory findings depend on the stage of disease[7] (Figure 4): In stage I, there are slightly low levels of 25-OH-D_3, low serum calcium, low normal serum phosphorus, elevated PTH (mild rickets). In stage II the 25-OH-D_3 levels are moderately low, and PTH returns serum calcium to normal through stimulation of 1,25-$(OH)_2D_3$ formation, but increases renal phosphate excretion. As serum calcium levels return to normal, PTH falls (moderate rickets). In stage III there are very low 25-OH-D_3 levels and low 1,25-$(OH)_2D_3$ levels, intestinal calcium malabsorption and bone resistance to PTH, hypocalcemia, hypophosphatemia and high PTH (severe rickets). Elevation of bone alkaline phosphatase and low urinary calcium may also be found.

Roentgenographic findings are primarily those of osteopenia, which is nonspecific and attributable to loss of bone mineral content. However, at least 30 percent of bone must be lost before osteopenia is apparent by the usual radiographic techniques. Osteomalacia may cause an indistinct, coarse appearance of bone trabeculae, but the radiographic hallmarks are Looser zones (pseudofractures) which are radiolucent bands found at the periosteal surface of ribs, pubic rami, scapulae and proximal ends of long bones. These represent stress fractures which heal poorly due to the mineralization defect; they may *light up* on bone scan and be mistaken for metastatic lesions. Subperiosteal resorption due to secondary hyperparathyroidism may also be present. Although there are more sensitive means of detecting bone loss, such as photon absorption densitometry, bone biopsy remains the most sensitive and specific means of diagnosing osteomalacia. After tetracycline labeling, histologically one sees an increase in osteoid volume with a decrease in the percentage of osteoid surface showing tetracycline fluorescence (the active mineralization front). Findings can be confirmed by the demonstration of low 25-OH-D_3 levels.[4]

Gastrointestinal Disease

The most common causes of simple vitamin D deficiency in the United States today are gastrointestinal disease. These have in common either primary malabsorption of dietary vitamin D or interruption of the enterohepatic circulation of 25-OH-D_3 with increased gastrointestinal losses.[4] The prevalence of osteomalacia in gastrointestinal disease is often not appreciated and therefore is underdiagnosed. After a mean of seven years following subtotal gastrectomy, there is a 25 percent incidence of bone disease which is often asymptomatic and suggested only by the finding of an elevated bone alkaline phosphatase. Although 25-OH-D_3 levels are low, the relative contributions of malabsorption and decreased dietary intake remain to be determined.[9,10] Malabsorption states[8,11] interfere with bile salt, micelle-mediated absorption and enterohepatic recycling of the fat soluble forms of vitamin D. Diseases such as gluten-sensitive enteropathy,[12] regional enteritis,[13] ileojejunal bypass[14] or pancreatic insufficiency have a high incidence of subclinical osteomalacia and low 25-OH-D_3 levels. Hepatic diseases such as Laennec cirrhosis or primary biliary cirrhosis cause vitamin D malabsorption secondary to bile salt deficiency, although hepatic parenchymal levels of 25-hydroxylase have not been determined.

Therapy with 5,000 to 10,000 IU per day of ergocalciferol (D_2) given orally is generally sufficient, but occasionally parenteral therapy is required.[8] Peak increase in 25-OH-D_3 levels may take one to three weeks, and levels should be monitored. Calcifediol (25-OH-D_3) may be available soon, and has the advantages of rapid onset and shorter half-life.

Increased excretion of 25-OH-D_3 may occur through the gastrointestinal tract due to binding of bile salts by cholestyramine therapy.[18] The nephrotic syndrome is associated with hypocalcemia, impaired intestinal calcium absorption, secondary hyperparathyroidism and low 25-OH-D_3 levels, due to losses of vitamin D binding globulin in urine.[19]

Anticonvulsant therapy,[20] particularly with diphenylhydantoin and phenobarbital, has been associated with hypocalcemia and osteomalacia. Plasma 25-OH-D_3 levels are low,[21] presumably secondary to increased degradation by hepatic microsomal enzymes induced by these drugs. Lack of exposure to sunlight by patients in hospitals or other institutions may also contribute. However, 1,25-$(OH)_2D_3$ levels are normal.[2] This finding suggests the importance of other 25-OH-D_3 derivatives in the maintenance of normal bone. A direct effect of these drugs on bone also cannot be excluded. Fortunately, 2,000 to 4,000 IU per day of D_2 given orally is effective therapy; the role of prophylaxis needs further study.

TABLE 1.—*Comparison of Vitamin D Preparations in Hypoparathyroid States**

	D_2	25-OH-D_3	1,25-$(OH)_2D_3$
Daily dose in hypoparathyroidism (μg)	750-3,000	50-200	0.5-2.0
Relative potency	1	15	1,500
Time to restore normocalcemia (weeks)	4-8	2-4	½-1
Time to reach maximum effect (weeks)	?4-10	?5-20	½-1
Persistence after cessation (weeks)	6-18	4-12	½-1

D_2 = ergocalciferol
25-OH-D_3 = calcifediol
1,25-$(OH)_2D_3$ = calcitriol

*Reproduced with permission from Frame B.[4]

The Cushing syndrome is an important cause of osteopenia,[22] with notable loss of trabecular bone resulting in characteristic vertebral compression and rib fractures. Patients at greatest risk for corticosteroid-induced osteopenia include children, the elderly (especially women) and patients with immobilizing rheumatic disorders.[24] Corticosteroids appear to decrease bone formation by a direct suppression of osteoblastic bone collagen synthesis; they increase bone resorption indirectly, through secondary hyperparathyroidism, by causing a dose-related malabsorption of intestinal calcium. Alternate day administration of prednisone or daily doses of less than 10 mg have no significant effect on calcium absorption. However, daily doses in excess of 15 mg result in a proportionate decrease in 25-OH-D_3 levels and calcium malabsorption.[25] Furthermore, in rats it has been shown that high dose corticosteroids decrease 1, 25-$(OH)_2D_3$ levels, although these measurements have not been made in humans. High doses of D_2 and 25-OH-D_3, but physiologic doses of 1,25-$(OH)_2D_3$ will correct the disturbance, suggesting 1-α-hydroxylase suppression in humans.[24] The role of vitamin D therapy in patients receiving high doses of corticosteroids has not yet been established in large clinical studies.

Hypoparathyroidism

The syndrome of hypoparathyroidism is characterized by hypocalcemia, hyperphosphatemia, neuromuscular irritability and tetany. The two major categories, hypoparathyroid (hormonopenic) and pseudohypoparathyroid (hormonoplethoric),[25] have in common malfunction of the calcium sensing arm of the homeostatic mechanism and reduction of 1,25-$(OH)_2D_3$ synthesis.[2] Past attempts at correction of hypocalcemia with

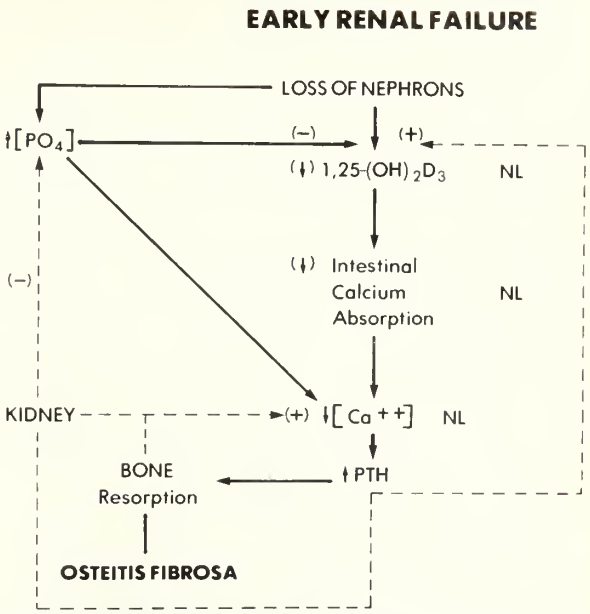

Figure 5.—Pathophysiology of osteodystrophy in early renal failure (glomerular filtration rate greater than 30 ml per minute): Solid lines (—) are direct consequences of nephron loss; dotted lines (----) are compensatory pathways. NL = normal levels.

pharmacologic doses of ergocalciferol (D_2) or dihydrotachysterol have been unsatisfactory and fraught with the hazard of prolonged toxicity[26] (Table 1). However, physiologic doses of 1,25-$(OH)_2D_3$ (calcitriol) or 1α-OH-D_3 have successfully increased intestinal calcium absorption and returned serum-ionized calcium to normal levels.[27-29] In the more common hormonopenic state, 1,25-$(OH)_2D_3$ deficiency is proportional to the degree of PTH deficiency and hyperphosphatemia, so vigorous efforts should be made to achieve normal serum phosphate levels through the use of phosphate binding gels.

Chronic Renal Failure

Although renal osteodystrophy has long been known to be a complication of chronic renal failure, it has emerged as a serious problem only recently, with prolonged patient survival made possible by dialysis. The pathogenesis of bone disease in renal failure is complex and multifactorial, but it can be best understood in terms of defects in mineral homeostasis involving PTH and a deficiency of vitamin D.[2,30]

According to the Bricker-Slatopolsky hypothesis,[30,31] one of the earliest and central abnormalities of renal failure is the decreased ability of the kidney to excrete phosphorus adequately (Figure 5). A loss of nephrons results in a rise in serum

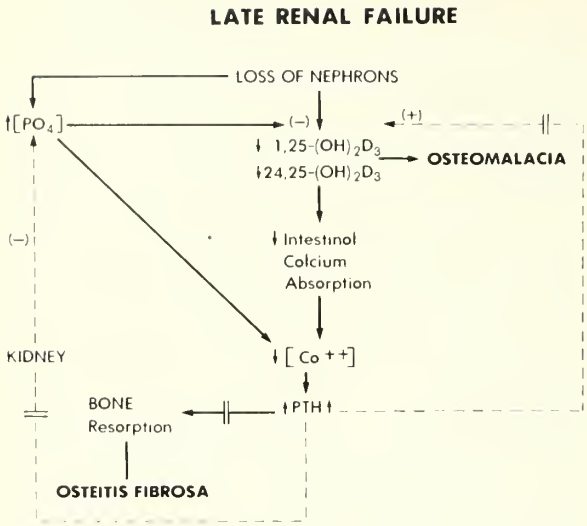

Figure 6.—Pathophysiology of osteodystrophy of late renal failure (glomerular filtration rate less than 30 ml per minute): Solid lines (—) are direct consequences of nephron loss; dotted lines (----) are compensatory pathways and → indicate blocked pathways.

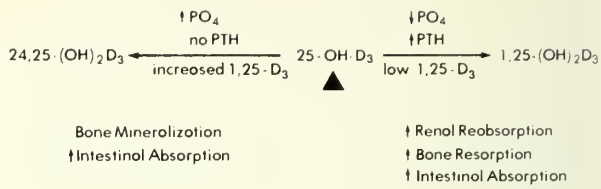

Figure 7.—Control point of 25-OH-D_3 metabolism and proposed consequences on calcium metabolism: Hypocalcemia (elevated parathyroid hormone levels) or hypophosphatemia favors 1,25-$(OH)_2D_3$ formation. Repleted state favors 24,25-$(OH)_2D_3$.

phosphate, a fall in ionized calcium and, consequently, an elevation of serum PTH levels at glomerular filtration rates of 60 to 80 ml per minute. At this stage, hyperparathyroidism without osteomalacia is usually found on bone biopsy.[32] Elevated PTH acts to bring serum calcium levels to within normal limits by increasing tubular phosphate excretion as well as maintaining normal serum 1,25-$(OH)_2D_3$ levels[30,33] and, hence, adequate intestinal calcium absorption and bone mobilization.

The next phase[34] of renal osteodystrophy develops at a glomerular filtration rate below 30 ml per minute, as nephron loss and phosphate retention reduce synthesis of 1,25-$(OH)_2D_3$ and the remaining tubules can no longer excrete the phosphate load despite elevated PTH levels (Figure 6). Low circulating 1,25-D_3 levels result in bone resistance to PTH and intestinal malabsorption of calcium, the hallmarks of the *vitamin D resistant state* of uremia. Hypocalcemia is further aggravated by poor dietary intake and decreased sunlight exposure, contributing to vitamin D deficiency.[2,3] However, the renal osteodystrophy of end-stage renal failure is more than just osteomalacia superimposed on osteitis fibrosa; there are poorly understood effects of toxins on protein collagen metabolism as well as very high PTH levels which contribute to the findings of osteoporosis and osteosclerosis.[34]

Therapy with physiologic doses of 1,25-$(OH)_2D_3$ (calcitriol, 0.5 mg per day) or 1α-OH-D_3 (1 to 2 μg per day)[35-39] has resulted in remarkable correction of biochemical abnormalities, with increased intestinal calcium absorption, normal levels of serum calcium and fall of PTH levels. Because of the short half-life of 1,25-$(OH)_2D_3$, the risk of vitamin D intoxication is much less than that of pharmacological doses of D_2 (Table 1). Episodes of hypercalcemia resolved in days rather than months. In addition, there was impressive clinical resolution of disabling bone pain and muscle weakness. However, serial bone biopsy studies showed improvement predominantly of the osteitis fibrosa component of bone disease, with much less effect on the osteomalacia. This unexpected finding cast serious doubts on whether 1,25-$(OH)_2D_3$ could account for all the biologic effects of vitamin D.

Although nephrectomy abolishes synthesis of 1,25-$(OH)_2D_3$, evidence of osteomalacia does not develop in all anephric patients.[40] In some patients, low 25-OH-D_3 levels seemed to correlate with osteomalacia.[41] In direct comparison of therapy with 25-OH-D_3 (calcifediol), 1,25-$(OH)_2D_3$ or 1α-OH-D_3 in patients with simple vitamin D deficient osteomalacia[42] or renal osteodystrophy,[43] 25-OH-D_3 was clearly superior in promoting bone mineralization. Also supraphysiologic 25-OH-D_3 has been shown to improve intestinal calcium absorption, raise serum calcium, lower alkaline phosphatase and PTH, and improve both symptoms and histology of osteomalacia in patients on dialysis.[34,44] This effect required levels of 25-OH-D_3 to be six times greater than normal; if hypercalcemia developed, it resolved in half a week to three weeks after withdrawal of the drug.

Which metabolite of 25-OH-D_3 is responsible for proper bone mineralization is a key question in vitamin D research today. There is accumulating evidence that 24,25-$(OH)_2D_3$ or some other 25-OH-D_3 metabolite may be important in the

TABLE 2.—*Optimal Therapy for Renal Osteodystrophy*

Early Renal Failure
(Glomerular filtration rate greater than 30 ml per minute)
Dietary phosphate binders
Insure adequate calcium and protein intake
? low dose vitamin D
Late Renal Failure
(Glomerular filtration rate less than 30 ml per minute)
Vigorous use of phosphate binders, especially before vitamin D therapy; monitor parathyroid hormone levels
Dialysis against bath of 6 to 8 mg per dl of free calcium
Adequate protein and calcium intake (1 gm per day elemental calcium)
Vitamin D metabolite therapy—25-OH-D_3 or 1,25-$(OH)_2D_3$ or both
Sunlight and exercise

process of bone mineralization[6] (Figure 7). 24, 25-$(OH)_2D_3$ is synthesized in both kidney and intestine,[1] and has been shown to increase intestinal calcium absorption while decreasing the serum concentrations of calcium and phosphorus. 24,25-$(OH)_2D_3$ is preferred in the repleted state to promote normal bone mineralization and the synthesis of hydroxyapatite ($Ca_{10}[PO_4]_6[OH]_2$). Animal studies have shown there to be a potent antirachitic effect of 24,25-$(OH)_2D_3$ and have even suggested a cooperative role with 1,25-$(OH)_2D_3$ in the normal mineralization process.[46] Further studies in humans will determine if 24, 25-$(OH)_2D_3$ is necessary for bone mineralization in patients with chronic renal failure. The therapeutic approach to renal osteodystrophy is outlined in Table 2.

Postmenopausal Osteoporosis

Approximately 1 million fractures per year occur in American women over the age of 45, of which some 700,000 are related to osteoporosis.[47] Fractures are a significant cause of morbidity and mortality in the geriatric population. The full-blown syndrome of back pain, skeletal fractures and loss of height is, however, seen in only 25 percent of those with decreased skeletal mass.[48,49]

Although the onset of osteoporosis and menopause are temporally related, as first pointed out by Albright,[50] the syndrome does not develop in all postmenopausal women. Other important factors are (1) age, (2) race (greater in whites), (3) skeletal mass at maturity, (4) physical activity, (5) nutrition (calcium intake, lactose intolerance), (6) vitamin D status and (7) hormonal status (estrogens).[48,51,52]

Abnormalities found in women with osteoporosis include increased rate of bone loss, decreased intestinal calcium absorption, slight hyperphosphatemia, normal or low PTH, fasting hypercalciuria, lower mean 1,25-$(OH)_2D_3$ levels and lower mean estrogen levels.[53,54] These findings, including the vitamin D abnormalities, are best explained by the model of Heaney.[55] He proposed that primary estrogen deficiency resulted in increased skeletal resorption because of increased sensitivity to the effects of PTH. This increased mobilization of bone results in transient elevation of serum calcium, suppression of PTH, decreased 1,25-$(OH)_2D_3$ levels and, hence, both decreased calcium absorption from intestine and loss of calcium through the kidney. Overall, there is negative calcium balance due to preferential mobilization of bone reserves, and secondary suppression of the PTH and vitamin D homeostatic mechanism.

Treatment with estrogen will raise 1,25-$(OH)_2D_3$, increase intestinal calcium absorption and prevent further bone loss without reversing the osteopenic state.[48,56-59] Modest doses of D_2 or physiologic doses of 1,25-$(OH)_2D_3$ will correct intestinal calcium malabsorption and decrease bone resorption.[54,60,61] However, the combination of sodium fluoride, calcium and vitamin D will stimulate bone formation and increase bone mass.[62] Since estrogens may carry an increased risk of endometrial carcinoma,[63] and fluoride causes pronounced gastrointestinal side-effects as well as possible abnormal bone histology, no current therapy for the established disease is ideal.[48,64] The best approach is preventive: ensure adequate sunlight, exercise, calcium intake and physiologic vitamin D supplementation. In considering estrogen therapy one must weigh the relative risk of fracture versus the possible development of cancer. Further study is required to define the roles of fluoride, calcitonin and vitamin D metabolites.

REFERENCES

1. DeLuca H: Vitamin D metabolism and function. Arch Intern Med 138:836-847, 1978

2. Favus M: Vitamin D physiology and some clinical aspects of the vitamin D endocrine system. Med Clin of North Amer 62: 1291-1317, 1978

3. Haussler M, McCain T: Basic and clinical concepts related to vitamin D metabolism and action. N Engl J Med 297:974-983, 1041-1050, 1977

4. Frame B, Parfitt A: Osteomalacia—Current concepts. Ann Intern Med 89:966-982, 1978

5. DeLuca H: Vitamin D endocrinology. Ann Intern Med 85: 367-377, 1976

6. Kanis J, Heyman G, Russell R, et al: Biological effects of 24,25-dihydroxycholecalciferol in man, *In* Norman AW, Schaefer K, Coburn JW, et al (Eds): Vitamin D: Biochemical, Chemical, and Clinical Aspects Related to Calcium Metabolism—Proceedings of Third Workshop on Vitamin D, Asilomar, Pacific Grove, CA, Jan 1977. Berlin, de Gruyter, 1977, pp 793-795

7. Arnaud S, Arnaud C, Bordier P, et al: The interrelationships between vitamin D and parathyroid hormone in disorders of mineral metabolism in man, *In* Norman AW, Schaefer K, Coburn JW, et al (Eds): Vitamin D and Problems Related to Uremic Bone Disease—Proceedings of Second Workshop on Vitamin D, Weisbaden, West Germany, Oct 1974. Berlin, de Gruyter, 1975, pp 397-410

8. Sitrin M, Meredith S, Rosenberg I: Vitamin D deficiency and bone disease in gastrointestinal disorders. Arch Intern Med 138: 886-888, 1978

9. Garrick R, Ireland A, Posen S: Bone abnormalities after gastric surgery. Ann Intern Med 75:221-225, 1971

10. Eddy R: Metabolic bone disease after gastrectomy. Am J Med 50:442-449, 1971

11. Stamp T: Intestinal absorption of 25-hydroxycholecalciferol. Lancet 2:121-123, 1974

12. Hepner G, Jowsey J, Arnaud C, et al: Osteomalacia and celiac disease. Amer J Med 65:1015-1020, 1978

13. Driscoll R, Meredith S, Wagonfeld J: Bone histology and vitamin D status in Crohn's disease—Assessment of vitamin D therapy. Gastroenterology 75:1051, 1977

14. Parfitt A, Miller M, Frome B, et al: Metabolic bone disease after intestinal by-pass for treatment of obesity. Ann Intern Med 89:193-199, 1978

15. Long R, Wills M, Skinner R: Serum 25-hydroxy-vitamin D in untreated parenchymal and cholestatic liver disease. Lancet 2: 650-652, 1976

16. Hahn T, Avioli L: Hepatic bioactivation of vitamin D and clinical implications, *In* Norman AW, Schaefer K, Coburn JW, et al (Eds): Vtamin D: Biochemical, Chemical, and Clinical Aspects Related to Calcium Metabolism. Berlin, de Gruyter, 1977, pp 737-741

17. Hepatic osteodystrophy. Lancet 1:988-989, 1977 (Editorial)

18. Thompson W, Thompson G: Effect of cholestyramine on the absorption of vitamin D_3 and calcium. Gut 10:717-722, 1969

19. Goldstein D, Yoshitake O, Kurokawa K: Blood levels of 25-hydroxy-vitamin D in nephrotic syndrome. Ann Intern Med 87:664-647, 1977

20. Hahn T, Avioli L: Anticonvulsant osteomalacia. Arch Intern Med 135:997-1000, 1975

21. Hahn T, Hendin B, Scharp C: Effect of chronic anticonvulsant therapy on serum 25-hydroxycalciferol levels in adults. N Engl J Med 287:900-904, 1972

22. Hahn T: Corticosteroid-induced osteopenia. Arch Intern Med 138:882-885, 1978

23. Hahn T, Hahn B: Osteopenia in patients with rheumatic diseases—Principles of diagnosis and therapy. Semin Arthritis Rheum 6:165-188, 1976

24. Klein R, Arnaud S, Gallagher J, et al: Intestinal calcium absorption in exogenous hypercortisonism. J Clin Invest 60:253-259, 1977

25. Nusynowitz M, Frame B, Kolb F: The spectrum of the hypoparathyroid states. Medicine 55:105-119, 1976

26. Avioli L: The therapeutic approach to hypoparathyroidism. Amer J Med 57:34-42, 1974

27. Russell R, Walton R, Smith R: 1,25-dihydroxycholecalciferol and 1α-hydroxycholecalciferol in hypoparathyroidism. Lancet 2: 14-17, 1974

28. Kooh S, Fraser D, DeLuca H, et al: Treatment of hypoparathyroidism and pseudohypoparathyroidism with metabolites of vitamin D—Evidence for impaired conversion of 25-hydroxy-vitamin D to 1α, 25-hydroxy-vitamin D. N Engl J Med 293:840-844, 1975

29. Davies M, Taylor C, Hill L: 1,25-dihydroxycholecalciferol in hypoparathyroidism. Lancet 1:55-58, 1977

30. Slatopolsky E, Rutherford E, Hruska K, et al: How important is phosphate in the pathogenesis of renal osteodystrophy? Arch Intern Med 138:848-852, 1978

31. Bricker N, Slatopolsky E, Reiss E: Calcium, phosphorus, and bone in renal disease and transplantation. Arch Intern Med 123:543-553, 1969

32. Malluche H, Ritz E, Lange H, et al: Bone histology in incipient and advanced renal failure. Kidney Int 9:355-362, 1975

33. Slatopolsky E, Gray R, DeLuca H: Low serum levels of $1,25(OH)_2D_3$ are not responsible for the development of secondary hyperparathyroidism in early renal failure, Fourth Workshop on Vitamin D. Berlin, Feb 1979, (abstract)

34. Bordier P, Marie P, Arnaud C: Evolution of renal osteodystrophy—Correlation of bone histomorphometry and serum and immunoreactive parathyroid hormone values before and after treatment with calcium carbonate or 25-hydroxycholecalciferol. Kidney Int, Suppl 2:102-112, 1975

35. Henderson R, Russell R, Ledingham, et al: Effects of 1,25-dihydroxycholecalciferol on calcium absorption, muscle weakness, and bone disease in chronic renal failure. Lancet 1:379-384, 1974

36. Brickman A, Sherrard D, Jowsey J, et al: 1,25-dihydroxycholecalciferol—Effect on skeletal lesions and plasma parathyroid hormone levels in uremic osteodystrophy. Arch Intern Med 134: 883-888, 1974

37. Berl T, Berns A, Huffer W, et al: 1,25-dihydroxycholecalciferol effects in chronic dialysis—A double-blind study. Ann Intern Med 88:774-780, 1978

38. Davie M, Chalmers M, Hunter J, et al: 1-alpha-hydroxycholecalciferol in chronic renal failure—Studies of the effect of oral doses. Ann Intern Med 84:281-285, 1976

39. Bordier P, Zingraff J, Gueris J, et al: The effect of $1\alpha(OH)D_3$ and $1\alpha 25(OH)_2D_3$ on the bone in patients with renal osteodystrophy. Amer J Med 64:101-107, 1978

40. Bordier P, Tun Chot S, Eastwood J, et al: Lack of histological evidence of vitamin D abnormality in the bones of anephric patients. Clin Sci 44:33-41, 1973

41. Eastwood J, Stamp T, Harris E: Vitamin D deficiency in the osteomalacia of chronic renal failure. Lancet 2:1209-1211, 1976

42. Bordier P, Ryckwaert A, Marie P, et al: Vitamin D metabolites and bone mineralization in man *In* Norman AW, Schaefer K, Coburn JW, et al (Eds): Vitamin D: Biochemical, Chemical, and Clinical Aspects Related to Calcium Metabolism. Berlin, de Gruyter, 1977 pp 897-911

43. Fournier A, Bordier P, Gueris J, et al: Comparison of 1α hydroxy-vitamin D_3 and 25 hydroxy-vitamin D_3 in the treatment of renal osteodystrophy—Greater effects of 25 hydroxy-vitamin D_3 in mineralizing bone, *In* Norman AW, Schaefer K, Coburn JW, et al (Eds): Vitamin D: Biochemical, Chemical, and Clinical Aspects Related to Calcium Metabolism. Berlin, de Gruyter, 1977, pp 667-679

44. Recker R, Schoenfeld P, Letteri J, et al: The efficacy of calcifediol in renal osteodystrophy. Arch Intern Med 138:857-863, 1978

45. Brickman A, Coburn J, Llach F: Biological actions of 24, $25(OH)_2D_3$ in normal and uremic man. Fourth Workshop on Vitamin D, Berlin, Feb 1979 (abstract)

46. Malluche H, Meyer-Sabellek W, Massry S, et al: Interaction of $1,25(OH)_2D_3$ and $24,25(OH)_2D_3$ on bone structure. Fourth Workshop on Vitamin D, Berlin, Feb 1979 (abstract)

47. Iskrant A, Smith R: Osteoporosis in women 45 years and over related to subsequent fractures. Public Health Rep 84:33-38, 1969

48. Thomson D, Frame B: Involutional osteopenia—Current concepts. Ann Intern Med 85:789-803, 1976

49. Wallach S: Management of osteoporosis. Hospital Practice, pp 91-98, Dec 1978

50. Albright F, Smith P, Richardson A: Postmenopausal osteoporosis—Its clinical features. JAMA 116:2465-2474, 1941

51. Aloia J, Cohn S, Ostuni J, et al: Prevention of involutional bone loss by exercise. Ann Intern Med 89:356-358, 1978

52. Newcomer A, Hodgson S, McGill D: Lactase deficiency—Prevalence in osteoporosis. Ann Intern Med 89:218-220, 1978

53. Heaney R: Vitamin D and osteoporosis, *In* Norman AW, Schaefer K, Coburn JW (Eds): Vitamin D: Biochemical, Chemical, and Clinical Aspects Related to Calcium Metabolism. Berlin, de Gruyter, 1977, pp 627-633

54. Riggs BL, Gallagher JC: Evidence for bihormonal deficiency state (estrogen and 1,25-dihydroxy-vitamin D) in patients with postmenopausal osteoporosis, *In* Norman AW, Schaefer K, Coburn JW (Eds): Vitamin D: Biochemical, Chemical, and Clinical Aspects Related to Calcium Metabolism. Berlin, de Gruyter, 1977, pp 639-643

55. Heaney R: A unified concept of osteoporosis (Editorial). Amer J Med 39:877-880, 1965

56. Aitken J, Hart D, Lindsay R: Oestrogen replacement therapy for prevention of osteoporosis after oophorectomy. Br Med J 3:515-518, 1973

57. Lindsay R, Aitken J, Anderson J, et al: Long-term prevention of postmenopausal osteoporosis by oestrogen. Lancet 1: 1038-1040, 1976

58. Gordon G: Postmenopausal osteoporosis—Toward resolution of the dilemma. West J Med 125:137-142, 1976

59. Recker R, Saville P, Heany R: Effect of estrogens and calcium carbonate on bone loss in postmenopausal women. Ann Intern Med 87:649-655, 1977

60. Riggs B, Gallagher J, DeLuca H: Serum vitamin D metabolites and intestinal calcium absorption in normal, elderly, and osteoporotic subjects. Fourth Workshop on Vitamin D, Berlin, Feb 1979 (abstract)

61. Gallagher J, Riggs B, DeLuca H: Effect of treatment with synthetic 1,25-dihydroxy-vitamin D in postmenopausal osteoporosis. Fourth Workshop on Vitamin D, Berlin, Feb 1979 (abstract)

62. Jowsey J, Riggs B, Kelly P: Effect of combined therapy with sodium fluoride, vitamin D and calcium in osteoporosis? Amer J Med 53:43-49, 1972

63. Antunes C, Stolley P, Rosenshein N, et al: Endometrial cancer and estrogen use. N Engl J Med 300:9-13, 1979

64. Avioli L: What to do with postmenopausal osteoporosis? (Editorial). Amer J Med 65:881-884, 1978

Important Advances in Clinical Medicine

Epitomes of Progress — Allergy

The Scientific Board of the California Medical Association presents the following inventory of items of progress in allergy. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in allergy which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Allergy of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Rhinitis Medicamentosa

RHINITIS MEDICAMENTOSA or medication rhinitis is one of the most frequent and, unfortunately, most overlooked causes of nasal stuffiness. The discomfort to persons with this condition cannot be minimized. Eating is hampered by an inability to breathe through the nose; however, the most distressing complaint is difficulty in sleeping. It is not uncommon for patients to be awakened three to four times a night by nasal obstruction. Although patients with allergic rhinitis are more prone to develop this syndrome, it occurs frequently in the general population.

The leading cause of rhinitis medicamentosa is excessive use of topical nasal decongestants. Virtually all nose drops and sprays, whether prescription or over-the-counter preparations, contain decongestants that are sympathomimetic amines. These preparations cause vasoconstriction, diminish nasal secretion of mucus and inhibit nasal ciliary action. Initial relief following their use is dramatic; however, all produce a *rebound* congestion as vasoconstriction diminishes. With prolonged use, their effects are paradoxical—the period of a patent nasal airway becomes progressively shorter, while nasal obstruction becomes longer lasting and more severe. This leads to dependence on the spray or drops, the patient usually buying two or three bottles at a time. Because one of the important functions of the nose is humidification of the air, patients also complain of a dry mouth and, often, a sore throat. The constant interruption of sleep leads to marked irritability and depression.

Antihypertensive drugs, especially those containing reserpine (even in small amounts), guanethidine, alpha methyldopa or propranolol can trigger the same sequence of symptoms. Other drugs or substances which have been implicated as causes of rhinitis medicamentosa include acetylsalicylic acid, cocaine, and estrogens; less frequently implicated substances include cromolyn sodium, alcohol and tobacco.

Rhinitis medicamentosa should be approached as an acute as well as a chronic problem. Simple awareness will often uncover the offending medication and the underlying condition that has precipitated the symptoms. However, during the acute phase, swelling may interfere with an adequate visualization of the nasal airway. Subsequent examination may show the presence of allergic rhinitis, nasal polyps or nasal septal obstruction which can be treated. The offending medication *must* be discontinued. An explanation of the *rebound problem* is useful in obtaining a patient's cooperation. The short-term use of dexamethasone intranasal

aerosol in decreasing doses for seven to ten days has been very effective in reducing inflammation of the nasal turbinates. Antihistamines and oral decongestants, because of their nonspecific drying action, tend to aggravate the condition initially, but may be useful later. Definitive therapy will depend on the underlying condition.

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REFERENCES

Blue JA: Rhinitis medicamentosa. Ann Allergy 26:425-429, Aug 1968

Baldwin RL: Rhinitis medicamentosa (an approach to treatment). J Med Assoc State Ala 47:33-35, Aug 1977

Recent Findings in Atopic Dermatitis

THE IMMUNOLOGY of atopic dermatitis has received much attention in the last ten years. Clinical observations as well as *in vivo* and *in vitro* studies have suggested that immunodeficiency may be involved in the pathogenesis of atopic dermatitis. An uncontrolled clinical study suggested that atopic dermatitis could be dramatically improved by levamisole, an anthelmintic and known immunostimulant. Two randomized, double-blind studies in children and adults failed to show any improvement in atopic dermatitis in the levamisole-treated groups.

We have examined the *in vitro* effect of levamisole on lymphocytes, neutrophils, basophils and platelets from patients with atopic dermatitis and levels of serum IgE greater than 1,000 IU per ml. Levamisole had no effect on basophil histamine release, platelet serotonin release, neutrophil chemotaxis and phagocytosis, T cell number and lymphocyte mitogenesis induced by phytohemagglutinin, concanavalin A or pokeweed mitogen. Thus, levamisole appears not to have any *in vivo* or *in vitro* value in atopic dermatitis.

Elevated serum levels of IgE remain the most consistent immunologic abnormality in this disease and understanding its regulation may be important for future therapeutic advances. Studies have shown that a small subpopulation of human lymphocytes have surface receptors for the constant function (Fc) portion of IgE. The function of these IgE-Fc receptor lymphocytes and their relationship to grossly elevated IgE levels in atopic dermatitis patients is now being investigated.

Regulation of IgE by helper and suppressor cells or soluble factors (or both) is another area under investigation. However, clinicians should continue to rely on current conventional therapy of atopic dermatitis until new approaches are confirmed and made available.

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REFERENCES

White CR, Hanifin JM: Levamisole therapy in atopic dermatitis: Randomized double-blind evaluation. Arch Dermatol 114: 1314-1315, Sep 1978

Alomar A, Gimenez-Camarasa JM, de Moragas JM: The use of levamisole in atopic dermatitis. Arch Dermatol 114:1316-1319, Sep 1978

Spiegelberg HL, O'Connor R, Simon RA, et al: IgE-Fc receptor bearing lymphocytes in patients with atopic disorders. J Clin Invest, In Press (Fed Proc 38:1088 [abstr], 1979)

Indications for Use of Beclomethasone Dipropionate (Vanceril)

BECLOMETHASONE DIPROPIONATE (Vanceril) is an inhalable synthetic corticosteroid useful in the control of chronic bronchial asthma. It apparently works by direct contact and is nearly insoluble with little systemic absorption. Sparing patients from systemic side-effects represents a great advance in management of the disease. When taken in its recommended dosage, it appears to cause no adrenal suppression or growth retardation in children.

At present, use of Vanceril in treating asthma is limited to selected patients whose conditions cannot be controlled with bronchodilators and other nonsteroid medications and patients with chronic severe asthma already dependent on systemic steroid therapy. Its use is not indicated in the treatment of status asthmaticus or acute asthmatic attacks.

During and after transfer from systemic corticosteroids to aerosol beclomethasone dipropionate, adrenal insufficiency has been reported. This can be obviated by warning the patient that during exposure to stressful situations such as trauma, surgical procedures or uncontrollable asthma, administration of systemic steroids should be resumed. Risk of adrenal insufficiency can be assessed with early morning resting cortisol levels and response to adrenocorticotropic hormone.

Other side-effects of Vanceril therapy include monilial infections of the mouth and pharynx in a small percentage of patients and reappearance of allergic manifestations such as rhinitis and eczema which were previously suppressed by systemic steroid therapy. Monilial infections may require antifungal treatment with nystatin (Mycostatin) discontinuation of Vanceril therapy.

The effects of the drug in active or quiescent tuberculosis and, in particular, the long-term

effects of aerosolized corticosteroids on various airway tissues remain to be determined.

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REFERENCES

Lovera J, Cooper DM, Collins-Wiliam C, et al: Clinical and physiological assessment of asthmatic children treated with beclomethasone dipropionate. J Allergy Clin Immunol 57:112-123, Feb 1976

Vogt F, Chervinsky P, Dwek J, et al: Beclomethasone dipropionate aerosol in the treatment of chronic bronchial asthma. J Allergy Clin Immunol 58:316-321, Aug 1976

Klein R, Waldman D, Kershnar H, et al: Treatment of chronic childhood asthma with beclomethasone dipropionate aerosol: I. A double-blind crossover trial in nonsteroid-dependent patients. Pediatrics 60:7-13, Jul 1977

Godfrey S, Balfour-Lynn L, Tooley M: A three- to five-year follow-up of the use of the aerosol steroid, beclomethasone dipropionate, in childhood asthma. J Allergy Clin Immunol 62: 335-339, Dec 1978

Mold Control

TWO SOURCES for mold spores growing indoors have been identified. The first and, generally, more important source (exogenous) originates from outdoors but is constantly introduced into homes. The second source (endogenous) originates indoors but varies greatly from house to house. Studies in Michigan, using the volumetric Andersen sampler during frost-free periods, indicated that indoor viable mold spore counts were approximately 25 percent of the outdoor counts. Indoor mold counts varied from 10 to over 20,000 spores per cu meter. Higher indoor counts were associated with high relative humidity within the home, and generally occurred in homes with central humidification.

Similar studies done in Southern California showed a statistically significant correlation between the following outdoor characteristics and high viable mold spore counts indoors: extensive shaded areas near the house, large quantities of organic debris (fallen leaves, grass not removed after cutting, hay, compost or stands of dried weeds and grass on the lot), poor landscape maintenance and previous indoor water problems. Two indoor characteristics associated with low indoor mold isolates were the presence of a central electrostatic filtration system and compliance with dust control. In homes with continuously operated electrostatic filters, the mean viable mold spore count was 155 per cu meter, while in homes with intermittently operated units, the mean mold spore count was 344 per cu meter. In control homes the mean count was 687 spores per cu meter. A less dramatic although still statistically significant reduction in mold spore isolates occurred in homes where dust control measures were being implemented.

The effect of air-conditioning on indoor mold levels was recently studied. A statistically significant reduction in mold spore isolates occurred in the air-conditioned homes, but no differences in the percent concentration of the major genera were noted. The investigators had expected a greater percent reduction in large mold spores if these were being trapped in the air-conditioner, but no reduction in smaller spores. Because all genera were reduced equally, the investigators felt that merely closing an air-conditioned home created a barrier to the ingress of outdoor molds resulting in lower indoor mold levels. They also noted reduction of mold isolates in air-conditioned homes with low indoor relative humidity.

It appears prudent to recommend the following program to minimize indoor mold spore concentrations. The amount of shade near a house should be reduced by avoiding plants too close to the building and by periodic pruning of trees and shrubs. Better landscape maintenance with removal of all dead vegetation within 150 to 200 feet of the house would be helpful. Dust control compliance is encouraged. Water damaged items including carpet, books, wallpaper and wicker baskets should be removed from the premises and the cause of any previous water problem corrected. Properly installed and operated central electrostatic filtration should significantly reduce the amount of viable indoor mold spores. Humidification devices including cold mist vaporizers are best avoided, especially in homes of mold-sensitive persons. Logically, use of a dehumidifier in damp areas should be helpful, but no studies have yet been carried out to verify this commonly held belief.

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REFERENCES

Solomon WR: Assessing fungus prevalence in domestic interiors. J Allergy Clin Immunol 56:235-242, Sep 1975

Solomon WR: A volumetric study of winter fungus prevalence in the air of midwestern homes. J Allergy Clin Immunol 57:46-55, Jan 1976

Kozak PP Jr, Gallup J, Cummins LH, et al: Factors of importance in determining the prevalence of indoor molds. Ann Allergy 43:88-94, Aug 1979

Hirsch DJ, Hirsch SR, Kalbfleisch JH: Effect of central air conditioning and meteorologic factors on indoor spore counts. J Allergy Clin Immunol 62:22-26, Jul 1978

Perspective on Asthma in Pregnancy

THERE IS NEARLY equal probability that maternal asthma will improve, remain the same or grow worse during pregnancy. Improvement tends to occur in the first trimester and deterioration in the second and third. Cases of severe steroid-dependent asthma are the most likely to cause deterioration in these women's conditions during their pregnancies. Slightly increased percentage rates of premature births, spontaneous abortions and new-

born deaths resulting from maternal asthma have been noted. The greatest danger to the fetus in maternal asthma is maternal hypoxia resulting in fetal hypoxia.

Several drugs used in the treatment of asthmatic patients are contraindicated in pregnancy. Preparations containing iodine may cause congenital goiter. Tetracyclines may stain the teeth. Sedatives in general are to be avoided because of their respiratory depressant effect. Hydroxyzine in large doses has been reported teratogenic in mice. The safety of the beta agonists such as terbutaline and metaproterenol has not been established in pregnancy.

Medications considered safe in the treatment of asthma during pregnancy include theophylline, ephedrine, cromolyn, penicillin and erythromycin. Corticosteroids used in the first trimester are known to cause cleft lip, cleft palate and skeletal deformities in experimental animals. They should be avoided if bronchospasm can be controlled without their use. In pregnant women with asthma who are steroid dependent, inhaled beclomethasone may allow reduction of dosage or even cessation of use of systemic steroids, although the safety of beclomethasone in pregnancy has not been established.

Because allergy skin testing and immunotherapy carry some risk of producing anaphylaxis, they should be used with special caution in pregnant patients, but need not be excluded. Ideally, asthma management should begin well in advance of contemplated pregnancies and control of this disorder should reduce both maternal and fetal morbidity and mortality.

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REFERENCES

Weinstein AM, Dubin BD, Podleski WK, et al: Asthma and pregnancy. JAMA 241:1161-1165, Mar 16, 1979

Greenberger P, Patterson R: Safety of therapy for allergic symptoms during pregnancy. Ann Intern Med 89:234-237, Aug 1978

Metzger WJ, Turner E, Patterson R: The safety of immunotherapy during pregnancy. J Allergy Clin Immunol 61:268-272, Apr 1978

Sulavik SB: Bronchial asthma, *In* Burrow GN, Ferris TF (Eds): Medical Complications During Pregnancy. Philadelphia, WB Saunders Co, 1975, pp 602-608

Reactions to Local Anesthetic Agents

SINCE FREUD AND KOLLER introduced cocaine into clinical use as a local anesthetic in 1884, various effects of local anesthetic agents have been described, including toxic effects of the drugs, systemic sympathomimetic stimulation, and vasovagal, local and allergic reactions. Rarely, preservatives such as paraben or methylparaben also may be incriminated.

Appropriate diagnoses are usually readily apparent by taking detailed histories of the episodes. Toxic effects are related to the total dose administered and include central nervous system stimulation (restlessness, dizziness and disorientation) or central nervous system depression (slurred speech, respiratory failure). Systemic sympathomimetic stimulation results from inclusion of epinephrine in the local anesthetic and includes anxiety, tremor, diaphoresis and tachycardia. Vasovagal symptoms may occur as a result of an injection of a local anesthetic; these may include apprehension, hyperventilation, hysteria and syncope. Localized swelling at the injection site often occurs and may be due to a local toxic effect of the anesthetic or to the procedure itself; however, especially when severe, a local IgE-mediated phenomenon cannot be ruled out. Pruritus, rhinorrhea, urticaria, angioedema and manifestations of bronchospasm, that is, cough and wheezing, are hallmarks of an allergic reaction. On careful scrutiny, however, only a small percentage of those presenting with questionable reactions will fit this category.

The clinical approach presumes a need to use an agent for either a necessary local procedure or for treatment of a cardiac arrhythmia. The risks inherent in the alternatives—whether to use a general anesthetic or not to use a lifesaving drug—clearly warrant provocative procedures and require an understanding of the classification of local anesthetics.

Although many pharmacologic agents have local anesthetic properties, all commonly used agents have a fundamental structure consisting of three parts: an amino group linked by an intermediate group to an aromatic residue, an ester (group I), or an amide or other bond (group II) serving to differentiate the two basic groups. Prominent among those in group I are benzocaine, butacaine (Butyn), chloroprocaine (Nesacaine), procaine (Novocain) and tetracaine (Pontocaine). These compounds will cross-react with each other. Reactions to compounds within this group have been reported much more frequently than to those within group II which represent a more diverse subset that lacks the ester bond. These compounds include dibucaine (Nupercaine), lidocaine (Xylocaine), prilocaine (Citanest), mepivacaine (Carbocaine) and proparacaine (Ophthaine). At present, it is presumed that those within group II do not cross-react with each other.

If a patient clearly has had an allergic or even

a moderate localized reaction to a drug, that specific drug should not be reused. Another non-cross-reacting drug should be chosen. After informed consent has been obtained and preparations made to treat any severe adverse reaction, titration intradermal skin testing may be used, with subsequent subcutaneous challenge using increasing amounts until from 0.5 to 1.0 ml is safely administered. There is disagreement as to the validity of skin testing in diagnosing or predicting immediate reactions. However, no one would disagree that it is still useful as a challenge technique. In recent studies, positive test results to anesthetics to which patients had not been previously exposed did not deter the authors from challenge, and no adverse reactions were encountered. In obvious toxic or vasovagal responses, or in reactions of questionable severity, the reuse of that agent will depend on the physician's confidence regarding the diagnosis.

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REFERENCES

Incaudo G, Shatz M, Patterson R, et al: Administration of local anesthetics to patients with a history of prior adverse reaction. J Allergy Clin Immol 61:339-345, May 1978
Aldrete JA, Johnson DA: Evaluation of intracutaneous testing for investigation of allergy to local anesthetic agents. Anesth Analg 49:173-183, Jan-Feb 1970
Luebke NH, Walker JA: Discussion of sensitivity to preservatives in anesthetics. J Am Dent Assoc 97:656-657, Oct 1978

Intravenous Radiocontrast Dye Reactions

ADVERSE REACTIONS to radiocontrast dyes (RCD) can range from innocuous vasomotor symptoms and rashes to life-threatening anaphylactoid reactions. The incidence of anaphylactoid reactions (any immediate reaction, whether urticaria or shock) after RCD has been reported at less than 2 percent, and the resultant mortality from one in 40,000 to one in 116,000 patients examined, or an estimated annual mortality of 500 patients. The mechanism for such reactions is unknown, but activation of the complement system, inactivation of enzyme systems, hyperosmolarity and antigen-antibody complexes have been suggested as possible explanations. The classic IgE-mediated anaphylactic mechanism has not been found. However, it is well established that RCD can release histamine both *in vivo* and *in vitro* from basophils and mast cells.

Initial studies using prophylactic antihistamines to avert the immediate reactions showed a decrease in the frequency and severity of reactions. More recent studies indicated that pretreatment with both steroids and antihistamines was successful in preventing serious reactions when the dyes were readministered to those who had had previous severe reactions. The risk of another anaphylactoid reaction in RCD-sensitive patients is unknown because patients may or may not react on subsequent exposure. Intravenous pretesting has been advocated to detect those patients who are at greatest risk for repeated serious reactions. However, intravenous pretesting has inherent risks, and its reliability has been disputed. Nevertheless, some practical guidelines for the management of RCD-reactive patients should be followed:

- After the physicians involved agree that the risk/benefit ratio supports the study, the patient should sign an informed consent in which the risks, options and potential benefits of the planned procedure are explained.
- Premedication with diphenhydramine (50 mg given intramuscularly) an hour before the study and prednisone (50 mg orally or equivalent parenteral dose) every six hours starting 18 hours before the procedure is indicated.
- A free-flowing intravenous line plus resuscitation equipment should be available to guard against the possibility of a serious reaction in spite of premedication.

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REFERENCES

Kelley JF, Patterson R, Lieberman P, et al: Radiographic contrast media studies in high-risk patients. J Allergy Clin Immunol 62:181-184, Sep 1978
Liberman P, Siegle RL, Taylor WW: Anaphylactoid reactions to iodinated contrast material. J Allergy Clin Immunol 63:174-180, Sep 1978
Yocum MW, Heller AM, Abels RI: Efficacy of intravenous pretesting and antihistamine prophylaxis in radiocontrast media-sensitive patients. J Allergy Clin Immunol 62:309-313, Nov 1978

Asthma and Sports

CAN MOST ASTHMATIC YOUNGSTERS participate in active sports? Yes. The attitude held by many parents, school instructors, coaches, counselors and even some physicians which prevents the asthmatic from participating in physical exercise should be changed.

Exercise-induced asthma or bronchospasm (EIA and EIB, respectively) classically occurs in a person during a rest period after exertion of at least five minutes, and may last as long as two hours. It occurs in nearly all asthmatic persons and in approximately 40 percent of those who have only allergic rhinitis or hayfever. The symptoms may include dyspnea, wheeze, chest tightness, increased mucus production, cough, choking or fatigue. Because of these restrictive symptoms persons with asthma are often told to modify their

active participation in sports. Others may offer excuses to avoid exercise due to fear or anxiety.

Exercises and physical fitness programs designed to improve diaphragmatic breathing apparently do not lessen the frequency, severity or duration of exercised-induced asthma attacks. Short exercise sessions of up to three minutes, however, often result in improved pulmonary function for several minutes. Consequently, short increments of running or other exercise can be tolerated by those in whom EIA may occur.

Exercise-induced asthma occurs equally in both allergic and nonallergic asthmatic persons. Cold or dry air, and airborne irritants and allergens can increase the probability of EIA developing. Generally, EIA appears to be directly related to the amount of exercise or work done by a person.

Most studies have shown that bronchodilators prevent EIA if given beforehand. Cromolyn sodium will also modify EIA in most allergic persons. Steroids, however, in any form have no apparent effect on EIA.

EIA can be prevented with theophylline given orally or beta adrenergic drugs given either orally or by inhalation 30 minutes before exercise. Cromolyn sodium must be given about an hour before exercise to be helpful.

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REFERENCES

Rebuck AS, Read J: Exercise-induced asthma. Lancet, 2:429, 1968

Sly RM, Heimlich EM, Busser RJ, et al: Exercise-induced bronchospasm: Effect of adrenergic or cholinergic blockade. J Allergy 40:93-99, Aug 1967

Katz RM, Whipp BJ, Heimlich RM, et al: Exercise-induced bronchospasm, ventilation, and blood gases in asthmatic children. J Allergy 47:148-158, Mar 1971

Eggleston PA, Bierman CW, Pierson WE, et al: A double-blind trial of the effect of cromolyn sodium on exercise-induced bronchospasm. J Allergy Clin Immunol 50:57-63, Jul 1972

Physical Agents That Mediate Urticaria

URTICARIA, characterized by localized skin edema or wheals, may be caused by any of several immunologic and nonimmunologic factors. Although the cause of chronic urticaria is never found in three fourths of cases, reactions due to physical agents such as pressure (dermatographia), heat and effort (cholinergic urticaria), cold, vibration and light (solar urticaria) can be identified and appropriately treated.

Dermatographia, one of the most common types of urticaria, is sometimes due to physical allergy. In certain cases, evidence indicates that it is mediated by, and can be passively transferred with, IgE. Dermatographia often accompanies urticaria induced by ohter causes.

Cholinergic urticaria is precipitated by heat, emotional stress and exercise as highly pruritic wheals (1 to 3 mm in size) with erythematous flare. Intradermal injection of methacholine (1:5,000) may produce a large wheal with satellites. This test, however, is not reliable enough for routine use because there are many false-negatives and some false-positives. Release of histamine into venous blood during attacks has been shown in some but not all of these patients. Activation of the cholinergic nervous system appears to be important in causing the wheals.

Solar urticaria is relatively uncommon. Several subtypes of solar urticaria are induced by light of wavelengths extending from 250 to 460 nM, with erythema and wheals developing in patients two to three minutes after exposure to sunlight. Repeated daily increments of solar exposure may prevent attacks.

Heat urticaria is characterized by swelling, redness and temperature dependence, and is not related to sweating or exertion. The lesions are nonpruritic and indurated. The phenomenon is associated with activation of complement via the alternate complement system. A pathologic reaction at the level of the venules with vascular endothelial damage has been described, but these lesions can be controlled by avoidance of heat. There is no role for antihistamines or corticosteroids in therapy.

Vibratory urticaria consists of prompt appearance of pruritus and swelling at the site of vibratory stimulation. The reaction is histamine mediated and is adequately controlled with antihistamine and avoidance of the source of vibratory stimuli. An autosomal dominant hereditary pattern has been described.

The familial form of *cold urticaria* is characterized by autosomal dominance, fever, arthralgia, leukocytosis and burning, erythematous papules. The ice cube test is negative and cannot be passively transferred. The papules occur about 30 minutes after cold exposure. A more common, acquired form of cold urticaria is associated with a positive ice cube test in all patients. In about 50 percent of patients, the test can be passively transferred with serum to normal persons. Urticaria in these persons is not associated with fever, arthralgia or leukocytosis. Cold-induced symptoms of systemic diseases such as cryoglobulinemia, cryofibrinogenemia, syphilis, connective tissue diseases and hematologic malignancies must be ruled out. Sporadic cold urticaria is definitely

associated with IgE-mediated release of histamine which can be inhibited with antihistamines. *Delayed cold urticaria* is a rare disease consisting of a painful induration occurring 12 to 24 hours after local cold exposure.

The treatment of urticaria induced by physical agents should be based primarily on removal of the cause. As with patients with other types of urticaria, these patients should be advised to minimize their exposure to alcohol, heat, acetylsalicylic acid, exertion and emotional stress. Topical agents and corticosteroids as well as attempts to desensitize patients with allergens are of no help in these situations. Appropriate sun screens may be of value in patients with solar urticaria, and antihistamines, including cyproheptadine and hydroxyzine, are of particular value in patients with dermatographia, cholinergic urticaria or cold urticaria.

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REFERENCES

Monroe EW, Jones HE: Urticaria: An updated review. Arch Dermatol 113:80-90, Jan 1977
Rhoades RB, Leifer KN, Cohan R, et al: Suppression of histamine-induced pruritus by three antihistaminic drugs. J Allergy Clin Immunol 55:180-185, Mar 1975

Factors That Influence Theophylline Metabolism

MANY ALLERGISTS in the United States consider theophylline to be the initial bronchodilator of choice. Serum levels of theophylline of 7 to 20 μg per ml are generally accepted as therapeutic. Although symptoms of toxicity may occur when the level of theophylline in the serum is in the therapeutic range, toxicity is generally associated with levels in excess of 20 μg per ml. It is incumbent on the physician using this valuable but potentially toxic drug to appreciate the number of factors that influence its biotransformation and clearance.

Body Weight

The apparent volume of distribution for theophylline is reduced in obese patients. When calculating dosage, one must use a patient's ideal weight to avoid toxicity.

Age

The dosage of theophylline required for children less than 1 year of age varies greatly. In this group, monitoring of serum levels of theophylline may be required to avoid problems with toxicity.

Children 1 to 8 years of age have average plasma clearance values above those noted for adults. The recommended oral dose for this group varies from 16 to 24 mg per kg of body weight per day. For those between 9 and 16 years of age, the recommended oral dose is 16 to 20 mg, and for adults it is 9.6 to 19 mg per kg of body weight per day.

Diet

Dietary methylxanthines, particularly caffeine, have been shown to interfere with theophylline elimination in normal persons. A decrease in theophylline elimination has also been noted in patients on high carbohydrate-low protein diets while a high protein-low carbohydrate diet increases theophylline elimination. Charcoal-broiled foods with a high polycyclic carbon content may increase the rate of theophylline biotransformation.

Diseases Altering Theophylline Metabolism

Theophylline clearance is affected by a variety of diseases involving the cardiorespiratory systems and the liver. These include congestive heart failure, acute pulmonary edema, chronic obstructive pulmonary disease, pneumonia, and cirrhosis and other hepatic diseases. Reduction in the dose of theophylline administered to these patients and careful monitoring of serum theophylline levels is required for proper management. Acute febrile illness has also been reported as a cause of transient increase in serum theophylline levels.

Smoking

In cigarette and marijuana smokers, there is a faster plasma theophylline clearance and a shorter half-life than in nonsmokers. Jusko and co-workers have shown that an additive increase in theophylline clearance occurs in those who smoke both substances.

An approximate reduction of 50 percent in theophylline clearance has been reported in patients who were receiving troleandomycin (250 mg four times daily). A similar but less pronounced effect due to erythromycin has been reported recently and appears due to reduced clearance and consequent prolonged half-life of theophylline. A reduction in theophylline dose is necessary for patients already receiving high-dose treatment when erythromycin or troleandomycin is coadministered. The possibility of other, as yet unrecognized, drug interactions with theophylline must be appreciated. If symptoms suggestive

of theophylline toxicity occur, a careful review of medications being administered should be made and the theophylline kinetics studied.

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REFERENCES

Ogilvie RI: Clinical pharmacokinetics of theophylline. Clin Pharmacokinet 3:267-293, Jul-Aug 1978

Jusko WJ, Schentag JJ, Clark JH, et al: Enhanced biotransformation of theophylline in marijuana and tobacco smokers. Clin Pharmacol Ther 24:406-410, Oct 1978

Landay RA, Gonzalez MA, Taylor JC: Effect of phenobarbital on theophylline disposition. J Allergy Clin Immunol 62:27-29, Jul 1978

Gastroesophageal Reflux and Asthma

RESPIRATORY MANIFESTATIONS of gastroesophageal (GE) reflux are increasingly being reported. In children and infants, reflux has been associated with bronchiolitis, pneumonitis and failure to thrive, while in adults bronchitis, laryngitis, bronchiectasis, atelectasis, fibrosis, pneumonia and intractable asthma are reported complications. The theories proposed to explain how GE reflux may cause or exacerbate asthma are: (1) microaspiration of gastric contents resulting in an exudative mucosal reaction, (2) vagal reflex arc from the esophagus to the lungs causing bronchoconstriction and (3) nonspecific irritant effect of microaspirates on a hyperactive bronchial airway.

The principal support of GE reflux-inducing asthma has come from reports of an increased association between hiatus hernia and asthma, and improvement of the respiratory systems following medical or surgical antireflux procedures. Unequivocal evidence that microaspiration occurs is lacking, but a recent study using a radioisotope technique showed gastropulmonary aspiration in two patients. Airway resistance increases after intraesophageal acid instillation in some asthma patients, in agreement with the vagal reflex arc theory.

GE reflux can be detected by techniques ranging from routine upper gastrointestinal series to more sensitive methods of cineradiography, esophagoscopy with biopsy, acid probe pH determination, acid perfusion study, esophageal manometry and isotope scintiscanning. University agreement on the criteria for diagnosing reflux is lacking. Further studies are needed to delineate the exact role of GE reflux in the pathophysiology of certain respiratory diseases. Until then clinicians should consider the diagnosis of GE reflux particularly in patients with recurrent pneumonitis or nocturnal asthma who also have gastrointestinal distress. Treatment is directed against factors that tend to decrease lower esophageal pressure, including smoking, the use of drugs such as theophylline, and the presence of anatomic abnormalities.

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REFERENCES

Christie DL, O'Grady LR, Mack DV: Incompetent lower esophageal sphincter and gastrointestinal reflux in recurrent acute pulmonary disease of infancy and childhood. J Pediatr 93:23-27, Jul 1978

Mays E: Intrinsic asthma in adults: Association with gastroesophageal reflux. JAMA 236:2626-2628, Dec 6, 1976

Mansfield LE, Stein MR: Gastrointestinal reflux and asthma: A possible reflex mechanism. Ann Allergy 41:224-226, Oct 1978

Reich S, Earley W, Ravin T, et al: Evaluation of gastropulmonary aspiration by a radioactive technique: Concise communication. J Nucl Med 18:1079-1081, Nov 1977

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EDITORIALS

Alcoholic Hypoglycemia and Ketosis

PLATIA AND HSU'S ARTICLE in this issue is an apt reminder that ketosis and hypoglycemia may develop in chronic alcohol abusers who are not diabetic.[1,2] Although Platia and Hsu's five patients had ketosis *and* hypoglycemia, the two abnormalities may occur separately in alcohol abusers. Indeed, in one of Miller's patients, who was admitted seven times with alcoholic ketoacidosis, there were initial serum glucose concentrations as low as 24 mg per dl and as high as 195.[3] It is not clear why just ketosis develops in some patients, just hypoglycemia in others and both in still others. Although some patients have had impaired liver function, that has not seemed to be essential in the pathogenesis of either the ketosis or hypoglycemia. Most of the patients have allegedly discontinued or severely curtailed their alcohol intake for several days before admission (and in some there has been no ethanol detectable in the blood). They have usually also stopped eating, because of anorexia, nausea, vomiting and severe abdominal pain. Indeed, acute starvation may be a major factor in the pathogenesis of both ketosis and hypoglycemia.

β-Hydroxybutyrate seems elevated disproportionately to acetoacetate, and the nitroprusside reaction has sometimes been only weakly positive (or even negative) despite considerably elevated β-hydroxybutyrate.[4,5] It is not known why β-hydroxybutyrate predominates so much over acetoacetate in this syndrome, in ratios even higher than in diabetic ketoacidosis, but coexisting lactic acidosis is apparently not the explanation. When ethanol is infused into starved rats' livers, the ratio of β-hydroxybutyrate to acetoacetate rises in the effluent.[6] However, most of the alcoholic ketotic patients apparently no longer have ethanol in their tissues. If the serum nitroprusside reaction is weakly positive or negative in a patient with an *increased-anion-gap metabolic acidosis* without uremia, the acidosis is difficult to ascribe to ketosis unless serum β-hydroxybutyrate can be rapidly measured and found elevated. Fortunately, whether such an *anion-gap-acidosis* is due to excess lactic acid, β-hydroxybutyric acid or some other unmeasured organic acid, need not alter the initial treatment with intravenously given fluid. Few patients with any of those types of metabolic acidosis will be harmed by intravenous administration of glucose solution, and some will be benefited, certainly so if they are also hypoglycemic. Of course, emergency care of such patients must include a search for specifically treatable causes of lactic acidosis, notably those due to hypovolemia and hypoperfusion.

The significance of the clinical and biochemical differences that have been noted in various series of alcoholic ketotics is difficult to judge because most of the series have been small. The differences are worth mentioning, however, because they may stimulate ideas about pathogenesis. Women have predominated in most of the series, but not in Platia and Hsu's nor in ours. Lactic acidosis, when present, has usually been due to incidentally coexisting hypoperfusion states, or occasionally acute alcoholic intoxication, and is not an essential feature of the syndrome. Blood pH has usually been low, except in our own series where many of the patients were not very acidemic (and some even alkalemic) owing to coexisting respiratory alkalosis (sometimes associated with delirium tremens), metabolic alkalosis (secondary to vomiting), or both.[5]

Alcoholic hypoglycemia seems mainly due to starvation, absent liver glycogen stores and impaired hepatic gluconeogenesis, although the explanation for the last remains unclear.[7] A conjecture that can be added to those previously suggested relates to the presumed inhibition of pyruvate dehydrogenase induced by starvation.[8,9] The consequent accumulation of pyruvate might promote conversion of glyceraldehyde-3-phosphate to diphosphoglycerate, thereby inhibiting gluconeogenesis. The pathogenesis of alcoholic ketosis is even less clear, most authors ascribing it to excess lipolytic factors (such as cortisol or growth hormone), or abnormalities of hepatic mitochondria. Serum cortisol concentrations have

often been elevated in the few patients with reported values, but cortisol is elevated in many seriously ill patients who are not ketotic. Although ethanol causes structural hepatic mitochondrial abnormalities,[10] if those abnormalities cause ketosis, why should the ketosis disappear so quickly after glucose administration? The mitochondrial structural abnormalities presumably do not. In nearly all the reported cases the patients have severely curtailed their food intake, usually for at least several days. Such starvation, superimposed on chronic malnutrition, together with the ketogenic effect of ethanol,[11] may be important in the pathogenesis of the ketosis (and the hypoglycemia). If that were the whole story, however, why do we not see more alcohol abusers with these syndromes? Perhaps the abnormalities are more common than we realize, but disappear when patients stop drinking, if only long enough to eat sufficient carbohydrate.

Treating the basic disorder—chronic alcohol abuse—is not very successful. The treatment of the hypoglycemia and ketosis, however, is; both respond rapidly to administration of glucose. Patients who are dehydrated, as many are because of vomiting, should also receive parenteral sodium chloride solutions, which may also promote the renal excretion of β-hydroxybutyrate and acetoacetate. Some patients, especially those with severe vomiting, may also require administration of potassium salts after renal function has been shown to be adequate. Whether some patients should also receive phosphate, especially because starved alcoholics may be phosphate-depleted and profound hypophosphatemia may develop during treatment (although initially they may have *hyper*-phosphatemia), has been discussed by Miller and colleagues.[3]

Alcoholic ketosis is defined as a syndrome occurring in nondiabetic persons. However, having diabetes mellitus surely does not protect a vomiting, starved chronic alcoholic from ketosis. Therefore, if a patient with presumed alcoholic ketosis is also diabetic—or if not known to be diabetic, develops severe hyperglycemia during treatment with glucose—it may be prudent to administer small doses of insulin to mitigate such hyperglycemia.

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REFERENCES

1. Dillon ES, Dyer WW, Smelo LS: Ketone acidosis in nondiabetic adults. Med Clin NA 24:1813-1822, 1940

2. Brown TM, Harvey AM: Spontaneous hypoglycemia in "smoke" drinkers. JAMA 117:12-15, 1941

3. Miller PD, Heinig RE, Waterhouse C: Treatment of alcoholic acidosis. Arch Intern Med 138:67-72, 1978

4. Cooperman MT, Davidoff F, Spark R, et al: Clinical studies of alcoholic ketoacidosis. Diabetes 23:433-439, 1974

5. Fulop M, Hoberman HD: Alcoholic ketosis. Diabetes 24: 785-790, 1975

6. Forsander OA, Maenpaa PH, Salaspuro MP: Influence of ethanol on the lactate/pyruvate and β-hydroxybutyrate/acetoacetate ratios in rat liver experiments. Acta Chem Scand 19:1770-1771, 1965

7. Madison LL: Ethanol-induced hypoglycemia, *In* Levine R, Luft R (Eds): Advances in Metabolic Disorders, Vol 3, pp 85-109, 1968

8. Garland PB, Newsholme EA, Randle PJ: Regulation of glucose uptake by muscle. Biochem J 93:665-678, 1964

9. Berger M, Hagg SA, Goodman MN, et al: Glucose metabolism in perfused skeletal muscle. Biochem J 158:191-202, 1976

10. Rubin E, Lieber CS: Experimental alcoholic hepatic injury in man: Ultrastructural changes. Fed Proc 26:1458-1467, 1967

11. Lefèvre A, Adler H, Lieber CS: Effect of ethanol on ketone metabolism. J Clin Invest 49, 1775-1782, 1970

Nationalized Health Care—A Juggernaut in 1981

WEBSTER DEFINES a juggernaut as "a massive inexorable force or object that crushes whatever is in its path." Some very recent events raise the possibility of a federal juggernaut for nationalized health care in 1981. If the person elected as President in 1980 rides the crest of an emotional wave of frustration with the present and of nostalgia for the past, and if that President were to have had a long experience in Congress and an essentially unchangeable personal commitment to nationalized health care, there could develop a situation much like that in 1965. A *landslide* presidential victory in 1964 permitted a legislatively skillful President to get a sweeping social program in health care enacted into law on a crash basis, with very little concern being given to its fiscal or other consequences. The consequences have now become familiar. There has been an unanticipated and frightening escalation in costs, in no small part due to clumsy and bungling attempts at planning, regulation and control of the health care enterprise. In all fairness the goal of more and better care for more people has been achieved but the real dollar cost of this achievement was neither calculated nor foreseen.

The possibility of a similar scenario for 1980 and 1981 seems real. The mood of the country appears at the moment to favor fiscal restraint and reducing the cost of government. Taxes, monetary inflation, unwanted dependence on foreign oil, and the rising price and uncertain availability of gasoline and other forms of energy are

all causing real concern. But there are also signs of smouldering frustration with these harsh realities and the growing restrictions they have begun to impose. One can sense that many people seem to be hoping, perhaps with a bit of nostalgia, for some sort of return or reincarnation of bygone times when money was more freely available and governmental spending seemed to solve any sort of problem. The young may especially resent the restrictions and discipline that are asked for, while the elderly may particularly resent the inflation and higher prices that erode their savings and carefully laid plans for retirement. Both are important voting blocks and they are joined by many other groups that stand to gain from government spending and further proliferation of government programs. This is highly combustible fuel for a health care juggernaut in 1981.

If nationalized health care is truly a good thing, then so be it. If it is not, then measures to counter or derail a possible juggernaut should begin soon. Most physicians and many others believe that nationalized health care is not in the long-term public interest and that there are better alternative solutions to the health care problems, which for whatever reasons seem to be so much a part of the public's agenda. There appear to be a number of basic points at issue:

- Is there a genuine need for nationalized health care? If so, what are the real or perceived problems in health care that are not now being met but which nationalized health care would solve? How could these needs be met if health care were not nationalized?

- The issue of health care costs is a major focus of attention. Would nationalized health care reduce or increase costs—and, if so, how? Can the existing health care enterprise or system control or reduce costs without nationalization—and, if so, how?

- Responsiveness is important in health care; that is, responsiveness to individual patient care needs and responsiveness to scientific and technologic advances in health care. Will nationalized health care be more or less responsive—and how? Can responsiveness in the existing health care enterprise be improved?

- Is autonomy and independence (freedom) in patient care important? And how important is autonomy and independence for the organizations and institutions involved in health care? What is to be done about the reality of *interdependence* among doctors, patients, and organizations and institutions involved in health care, as well as the role and responsibility of government which have developed so greatly since 1965?

It is suggested that the above are among the fundamental issues in health care to be addressed at this time.

This writer believes that the issue of autonomy and independence (call it freedom if you will) within an inescapable reality of de facto interdependence (which after all really calls for some kind of regulating or control mechanisms if an interdependent system is to work smoothly) is the core issue to be addressed. If some workable and acceptable accommodation can be found for this fundamental issue, it seems likely that the others will begin to fall into place. Basically the regulations or controls that are needed for any interdependent social system to work smoothly must be either external—that is, imposed from the outside—or internal—evolving within the system itself. The present proponents of nationalized health care appear to assume that the regulation and control will be carried out by the federal government through laws and bureaucratic rules, and therefore imposed from the outside. This approach by definition cannot help but restrict, if not destroy, freedom and independence for patients, physicians, and the many organizations and institutions within the health care system. But, given the interdependence that is now a fact of life, is there a better alternative? Perhaps there is. If there is, and if autonomy and independence are to be preserved for all concerned, then one must look within the system for voluntary collaboration and coordination (which can be accomplished without loss of autonomy or independence) to find acceptable and workable solutions to health care problems within the realities of the interdependence among the parts of the system.

If all this is indeed the case, as it seems to be, then it is time for the leadership of a still somewhat free and independent health care enterprise to study collaboratively each of the issues listed above, and no doubt others, and to develop a response or a plan from within the existing health care system to deal more efficiently and effectively with each of the problems that nationalized health care would be expected to solve. Perhaps some sort of summit conference of the national health care enterprise is needed as an initial step, to begin a collaborative effort to (1) identify and

define the problems which must be solved, (2) decide what needs to be done and (3) develop a strategy of collaboration and coordination to get it done. This is long overdue and should now be accomplished as soon as possible, before any sort of nationalized health care juggernaut begins to gather momentum in the nation. Actually there may be very little time to spare. The scenario may have already started.

—MSMW

Phenylketonuria and Its Variants

OF ALL THE 150 or 200 inborn errors of metabolism known today, phenylketonuria (PKU) is the best known and the most studied. The reasons for this are clear: PKU is one of the commonest of these diseases (one in about 14,000 live births in the United States, even commoner in some ethnic groups), if untreated it leads to lifelong severe mental retardation (more devastating to the average family than, say, death in infancy) and an effective treatment is readily available. It is this last feature that has led, over the last 30 years, to the great interest in PKU among pediatricians and has caused many states to introduce screening of all neonates, as described by Dr. Charles Parker elsewhere in this issue. We can control the clinical features of PKU better than those of most inborn errors of metabolism—it is paradoxical though rewarding that our very success in treating PKU will in future severely limit opportunities to study the natural history of the disease. On the purely scientific side there have also been advances, though these have been slower than in clinical management and screening.

The collaborative study of children treated for PKU, referred to by Dr. Parker, was originally set up to determine whether dietary treatment had any value. Although at the time some felt this to be supererogatory, much valuable information has been produced by the study and our knowledge of PKU has been materially advanced by it. In the last few years, the collaborative study has been concentrating on when the dietary treatment should be terminated. Even in the early 1950's, pediatricians hoped that a normal diet could be resumed after a few years and some were courageous enough (or were forced by circumstances) to try the experiment. Scattered conflicting reports of the effects of terminating treatment appeared in the literature and the collaborative study has started a systematic investigation.

The low-phenylalanine diet was introduced because it was hypothesized that the high concentration of phenylalanine in the blood damaged the brain from soon after birth onwards and, as often happens with brain damage in infancy, this showed itself as global mental retardation.[1] However, a similar insult to a more mature brain would be expected to produce a different spectrum of signs and symptoms; although there might well be intellectual deterioration—that is, dementia—this would probably be relatively slow, and a more sensitive indicator of late onset phenylalanine intoxication would be desirable. Intelligence quotient tests were first used in the early 1950's for following effects of dietary treatment[1] and have been widely used since. They are probably the best indicators we have of brain damage caused by hyperphenylalaninemia in early infancy; however, there are better tests for the brain damage that might result from late onset phenylalanine intoxication—for example, tests of attention span, the categories subtest of the Reitan-Halstead battery, and structured or semistructured psychiatric interviews.

The early literature reported a handful of cases of "atypical PKU": cases of persons with normal or near normal intelligence quotients and with substantially raised blood phenylalanine levels and urinary excretion of phenylpyruvic acid and other "abnormal" phenylalanine metabolites. With improved laboratory techniques it was shown that these persons had blood phenylalanine concentrations well below those of typical patients with PKU, though considerably above the normal. The frequency with which these cases occurred became apparent when screening of the newborn was introduced—about one in 30,000 live births or one in three of all those with hyperphenylalaninemia in the United States were affected. These cases were labeled hyperphenylalaninemia variants or *hyper-phe*. Phenylalanine hydroxylase is the enzyme that normally converts phenylalanine to tyrosine but is absent or inactive in persons with typical PKU; in those with variant forms of hyperphenylalaninemia there is appreciable phenylalanine hydroxylase activity in the liver, though far less than in the normal. In some of these persons there is evidence suggesting a qualitatively altered phenylalanine hydroxylase which in turn suggests a structural gene mutation,

in others there is insufficient evidence to decide whether a structural gene or a regulator gene has undergone mutation. Most patients with variant forms of hyperphenylalaninemia do not require dietary treatment after the first few months of life, although the decision whether to treat, and for how long, requires both careful investigation and clinical judgment. Laboratory findings range from the almost normal to those of typical PKU with no discontinuities and, as far as we know, clinical effects parallel the blood phenylalanine concentrations. As Dr. Parker points out, whether one classifies a child as having PKU or as *hyperphe* depends on an arbitrary set of criteria and near the borderline should not involve any difference in treatment.

Studies of phenylalanine hydroxylase have advanced at a snail's pace since the identification of this enzyme by Mitoma and colleagues[2] and by Wallace and co-workers[3] in 1957. Only in the last five or six years have a number of laboratories in different countries taken up the problem and progress has accelerated. Two groups, Danks, Cotton and associates[4,5] in Melbourne, Australia, and Bessman, Barranger, Parker and co-workers in Los Angeles[6,7] have used innovative approaches in which the crude liver homogenate supernatant is subjected to a single chromatographic separation without the laborious preliminary protein separations usually involved in isolating enzymes. The Australian group uses affinity chromatography; that is, the ability of phenylalanine hydroxylase to bind specifically to its cofactor which has been immobilized by binding to sepharose. The Los Angeles group uses columns of calcium phosphate gel. Both methods have the advantages of speed and simplicity—many samples can be investigated in the time it takes to make a single preparation by conventional methods. However, there are difficulties in the interpretation of the results obtained using these novel techniques and, in both cases, the phenylalanine hydroxylase preparations need to be compared with the enzyme prepared by traditional methods, which has not yet been done. Nevertheless, affinity chromatography is a powerful technique and it seems likely that much of our information on phenylalanine hydroxylase over the next few years will come from the Australian group.

Several workers have reported that phenylalanine hydroxylase, as isolated, is polydisperse, at least two forms of different molecular weights or isoelectric point (net charge) or both being present. This is, at present, the area of greatest obscurity. One group[8] found that filtration through glass wool, a technique that splits certain complexes, converted the higher molecular weight forms to the lower molecular weight (about 108,000) form also present. Many workers are approaching the conclusion that the relevant gene codes for a polypeptide of molecular weight about 54,000, that a dimer of this polypeptide is enzymically active and that higher molecular weight and other forms of the enzyme are either the results of posttranslational changes or artifacts arising during isolation. Phosphorylated forms of the enzyme have been described, though it is not clear that these play any part in regulating enzymic activity *in vivo*. Phosphorylated enzymes with their relevant kinases and phosphatases generally are associated with metabolism of, for example, glycogen (where the body may be subjected to sudden loads or demands and rapid regulation of enzymic activity is necessary) but there is no evidence that phenylalanine hydroxylase falls into this category.

The three forms of phenylalanine hydroxylase, pi, kappa and upsilon, described by Dr. Parker probably represent posttranslational changes in the phenylalanine hydroxylase molecule resulting in an alteration of net charge. Because the molecular weights are reported[7] to be in the range 135,000 to 150,000, the dimer molecule must be complexed with some molecule or molecules of total weight 27,000 to 42,000. The term *isozyme* should not be applied to such posttranslational complexes; conventionally *isozymes* or *isoenzymes* are taken to be two or more different protein molecules with similar enzymic activity coded for by two or more nonallelic genes, and usually occurring in different tissues—an example is the pyruvate kinases of erythrocytes and leucocytes. The term isozyme is not applied to the different enzymes produced by various mutations of a single structural gene (the single locus multiple allele case). Because PKU and the variant forms of hyperphenylalaninemia are genetically determined—that is, are the results of gene mutation—it is difficult to see how variations in the relative amounts of the three posttranslational complexes, pi, kappa and upsilon, can be related to different degrees of severity of the disease. The suggestion that we are dealing with multiple loci rather than multiple alleles[7] runs counter to all the genetic evidence. It could be postulated that a structural gene mutation might lead to a protein with a re-

duced tendency to form certain complexes, but there is no evidence on this point and, in any case, its possible relevance to any clinical features is obscure. Possibly more relevant is recent evidence that formation of these complexes is under hormonal control.[9]

Dr. Bessman has long been critical of the dietary treatment of PKU and of the intoxication hypothesis on which the treatment is based. He has put forward an alternative, the justification hypothesis.[10] This postulates that, because heterozygotes for PKU have only half the normal amount of phenylalanine hydroxylase, a pregnant heterozygote will supply less than the optimum amount of tyrosine to all her offspring *in utero* and, should a fetus be homozygous for the PKU gene, it will be unable to convert phenylalanine to tyrosine and will have severe tyrosine deficiency. According to the justification hypothesis the severe or profound mental retardation of PKU results from this tyrosine deficiency *in utero*. There is, however, strong evidence that such fetuses do not have tyrosine deprivation *in utero* which, as far as PKU is concerned, disproves the justification hypothesis. Many hundreds of infants with PKU have by now been treated with the low-phenylalanine diet and are mentally normal. This would not be expected if the mental retardation of untreated PKU were the result of events *in utero*. Fasting plasma tyrosine concentrations in heterozygotes (1.042 ± 0.23 mg per 100 ml, $n = 34$) were not greatly different from those in normal controls (1.127 ± 0.19 mg per 100 ml, $n = 39$).[11] There is little information on blood tyrosine levels during pregnancy or on variations during the course of the day.

Tyrosine is an essential amino acid for those with PKU—before as well as after birth. Hence tyrosine deficiency *in utero,* like protein deficiency, would result in a low birth weight in relation to gestational age. The four studies of birth weights of infants born to mothers who are obligate heterozygotes for PKU all showed no differences between these infants and normal controls,[12-15] moreover there were no differences between the birth weights of infants with PKU and of their unaffected siblings of whom presumably two thirds were heterozygotes and a third homozygous normal. What evidence there is suggests that, if partial deprivation of protein or an essential amino acid occurs in fetal life, the brain is to some extent spared relative to other organs; there is no reason to expect that tyrosine deficiency would affect the brain but leave the body weight unaffected and, in fact, the head circumferences of infants with PKU are normal at birth.[15] In older untreated patients with PKU there is pronounced microcephaly, which must arise postnatally. However, those treated with a low-phenylalanine diet since earliest infancy have normal head circumferences. Hence, the justification hypothesis should be rejected for PKU. There is no evidence for tyrosine deficiency *in utero* or that this causes mental retardation either in homozygotes or heterozygotes. The justification hypothesis, however, may be correct for some other aminoacidopathies. Each condition will have to be investigated separately.

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REFERENCES

1. Woolf LI, Griffiths R, Moncrieff AA: Treatment of phenylketonuria with a diet low in phenylalanine. Brit Med J 1:57-64, 1955

2. Mitoma C, Auld RM, Udenfriend S: On the nature of the enzymatic defect in phenylpyruvic oligophrenia. Proc Soc Exp Biol Med 94:634-635, 1957

3. Wallace HW, Moldave K, Meister A: Studies on the conversion of phenylalanine to tyrosine in phenylpyruvic oligophrenia. Proc Soc Exp Biol Med 94:632-633, 1957

4. Cotton RGH, Danks DM: Purification of inactive phenylalanine hydroxylase protein from liver in classical phenylketonuria. Nature (Lond) 260:63-64, 1976

5. Cotton RGH, Grattan PJ: Phenylalanine hydroxylase of Macaca irus, a simple purification by affinity chromatography. Eur J Biochem 60:427-430, 1975

6. Barranger JA, Geiger PS, Huzino A, et al: Isoenzymes of phenylalanine hydroxylase. Science 175:903-905, 1972

7. Barranger JA: The implications of multiple forms of phenylalanine hydroxylase in phenylketonuria and related diseases of phenylalanine metabolism. Biochem Med 15:55-86, 1976

8. Woo SLC, Gillam SS, Woolf LI: The isolation and properties of phenylalanine hydroxylase from human liver. Biochem J 139:741-749, 1974

9. Miller MR, Shiman R: Hydrocortisone induction of phenylalanine hydroxylase isozymes in cultured hepatoma cells. Biochem Biophys Res Comm 68:740-745, 1976

10. Bessman SP: Genetic failure of fetal amino acid "justification": A common basis for many forms of metabolic, nutritional and "non-specific" mental retardation. J Pediat 81:834-842, 1972

11. Woolf LI, Cranston WI, Goodwin BL: Genetics of phenylketonuria. Nature (Lond) 213:882-883, 1967

12. Woolf LI: A study of the cause of the high incidence of phenylketonuria in Ireland and West Scotland. J Ir Med Assoc 69:398-401, 1976

13. Rothman KJ, Pueschel SN: Birthweight of children with phenylketonuria. Pediatrics 58:842-844, 1976

14. Smith I, Carter CO, Wolff OH: Heterozygote advantage for the phenylketonuria allele. J Med Genet 15:246-248, 1978

15. Holm VA, Kronmal RA, Williamson M, et al: Physical growth in phenylketonuria: II. growth of treated children in the PKU collaborative study from birth to 4 years of age. Pediatrics 63:700-707, 1979

CASE REPORTS

Refer to: Aelony Y, Finegold SM: Serious infectious complications after flexible fiberoptic bronchoscopy. West J Med 131:327-333, Oct 1979

Serious Infectious Complications After Flexible Fiberoptic Bronchoscopy

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SINCE FLEXIBLE FIBEROPTIC BRONCHOSCOPY was introduced in the late 1960's, a number of surveys have emphasized the paucity of serious complications related to the procedure. A mail survey turned up only two reports of pneumonia following 24,000 bronchoscopic procedures.[1] In a second survey by mail, Suratt and co-workers were able to collect information on 48,000 bronchoscopies.[2] Twelve deaths and 158 serious complications were recorded, yet not a single infectious complication was mentioned. In a prospective study of 100 patients by Pereira and associates,[3] 16 cases of fever and six cases of parenchymal infiltrates were noted. However, their study suggests a benign course for these infiltrates, in that all but one patient (15 of 16) recovered "without antimicrobial therapy." The report below details three instances in which pulmonary infection after fiberoptic bronchoscopy resulted in serious morbidity requiring aggressive antimicrobial therapy.

Reports of Cases

CASE 1. A 25-year-old woman was seen on March 29, 1975, because of a loculated pleural effusion posterior to the superior segment of the left lower lobe (LB6). Two years before, a routine roentgenogram had shown a left midlung infiltrate and the patient had been admitted to a university hospital. Extensive workup there failed to find the cause of the infiltrate and the patient was treated empirically with antituberculous drugs. She was referred to one of the authors (Y.A.) when follow-up films showed a gradual increase in density and size of the known abnormality (Figure 1).

The patient was asymptomatic. She said that chills, fevers, night sweats, malaise, anorexia, gastrointestinal symptoms, weight loss, cough, sputum, wheezing, chest pain or dyspnea had not occurred. Past medical history was negative except for occasional childhood asthma and eczema. She had smoked one pack of cigarettes a day for six years. Abnormalities on physical examination were confined to the chest. Auscultation and percussion showed focal dullness, decreased tactile fremitus, dry rales and tubular breath sounds over a small area below the left scapular tip. Roentgenograms showed a dense, bilobate mass in the same area with several centimeters of normal-appearing lung separating the mass from the diaphragm. Initial evaluation showed 8,200 leukocytes per cu mm, erythrocyte sedimentation rate of 38 mm per hour (Wintrobe) and hemoglobin of 13.1 grams per dl. Histoplasma and coccidioidal serological tests were negative; sputum cultures were negative for routine bacteria, acid fast bacilli and fungi.

A Cope needle biopsy yielded pleura with nonspecific inflammation. Also 500 ml of thin yellow pleural fluid of low viscosity was removed which contained 2,000 leukocytes per cu mm with 8 percent polymorphonucleocytes, 68 percent mononuclear cells and 24 percent eosinophils; the protein content was 4.5 grams per dl. Gram stain was negative and both the fluid and pleural tissue failed to yield organisms on routine, anaerobic, fungal and mycobacterial culture. Postthoracentesis films showed a 10 percent pneumothorax and some spillage of the loculated fluid into the previously clear left costophrenic angle (Figure 1).

Five hours later, the patient was still asymptomatic and fiberoptic bronchoscopic examination

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was carried out uneventfully with an Olympus BF-5B2 instrument through an orotracheal tube. No bronchial secretions or endobronchial abnormalities were seen. The LB6 subsegments were brushed for culture specimens. Three transbronchial lung biopsy specimens were obtained from the superior and inferior divisions of LB6. Bronchial washings and brushings subsequently grew alpha hemolytic streptococci and anaerobic streptococci; tuberculosis and fungus cultures were negative. No pleuritic pain was reported by the patient and postbronchoscopy films showed no change. She returned to work the following day and felt well until four days later when an evening fever was noted.

The patient was admitted to hospital acutely ill on April 7 (six days after the bronchoscopy) with a temperature of 38.9°C (102°F). During the first 16 days in the hospital, progressive anorexia, nausea, vomiting and weight loss occurred. During this period she had no cough. Temperature rose to 41°C (106°F). Breath sounds were diminished on the left side of the chest posteriorly. Roentgenograms showed an increasingly dense left hemithorax (see Figure 2) which changed little after multiple thoracenteses. Pleural taps produced fluid of similar character to that noted above, with the highest leukocyte count equal to 3,300 cells per cu mm of fluid. Peripheral leukocyte count rose to 14,000 cells per cu mm with a shift to the left. Multiple Gram stains and aerobic and anaerobic cultures were negative. The course of her disease was unaffected by parenteral administration of ampicillin and 10 million units per day of aqueous penicillin G.

On the 17th hospital day the patient suddenly coughed violently during bronchography producing more than 500 ml of putrid, white, gray and green thin pus. Smears of pus contained a full field of polymorphonuclear leukocytes and at least five types of pleomorphic Gram negative and Gram positive organisms; many Cryptococcus-like organisms were seen on India ink examination. Aerobic cultures grew Hemophilus influenzae. Transtracheal aspiration for anaerobic culture was omitted because of severe peritracheal emphysema following the bronchogram. The patient's toxic course dramatically reversed following institution of clindamycin given intravenously and postural drainage for the now evident putrid lung abscess.

Belatedly, special stains were applied to the original transbronchial lung biopsy specimens of April 1, and large numbers of cryptococcal organisms were shown scattered throughout necrotic lung tissue. The diagnosis of chronic pulmonary cryptococcosis was confirmed when the Center for Disease Control reported that the serum latex agglutination titer for cryptococcal antigen was 1:1024. Examination of the cerebrospinal fluid showed no abnormalities. Ultimately, treatment was carried out with intravenously administered

Figure 1.—Case 1. **A**, posteroanterior and **B**, lateral films of the chest in March 1975. These are representative of the roentgenograms done between January and April 1975, the only major difference being that the left costophrenic angle shows blunting now just subsequent to the thoracentesis, which was not present before that procedure.

amphotericin B and orally given 5-fluorocytosine[4] for cryptococcosis. Follow-up through September 1978 found the patient to be well, with stable radiographic residual changes (Figure 3).

In summary, a chronic, indolent, asymptomatic, localized, cryptococcal pneumonitis with sympathetic pleural effusion was present in this case. Four days after bronchoscopy, signs of an acute infectious process developed which culminated in an anaerobic lung abscess. The presence of cryptococci and the absence of bacteria on the lung biopsy specimens, together with the clinical history, leave little doubt that the anaerobic infection began after the bronchoscopy. The anaerobic infection undoubtedly occurred from seeding of upper-airway organisms into necrotic lung tissue during transbronchial biopsy.

CASE 2. A 41-year-old woman had smoked one pack of cigarettes per day for 20 years and usually coughed up white "mucus" in the morning. Intermittent wheezing attacks had occurred all her life, mostly during the fall hay fever seasons. She had been treated three times for *walking* pneumonia. In March 1973 she fractured the distal femur in an auto accident. Despite several surgical procedures, union of the femur failed to occur. At the time of the accident, a right upper lobe infiltrate was noted and treated as bacterial pneumonia. Roentgenograms did not change on follow-up through June 1974. A preoperative film in July 1974, however, showed increased size of the lesion and cavitation (Figure 4). Outpatient workup included negative tuberculin skin test through 250 TU; negative coccidioidomycosis skin test and serology; positive histoplasmin skin test, and positive histoplasmosis complement fixation of 1:4 (yeast phase). Erythrocyte sedimentation rate was 10. Sputum cultures and cytologies were negative.

In September 1974 the patient felt well except for pain in the leg. Physical examination gave normal findings except for the fractured leg. Spirometry showed a mild to moderate obstructive defect, which improved greatly after a bronchodilator. Fiberoptic bronchoscopy through an orotracheal tube was remarkable only for some tenacious yellow material exuding from the anterior segment of the right upper lobe (ASRUL). This exudate was aspirated and sent along with bronchial brushings for mycobacterial and fungal cultures and cytological analysis. Two brushes were passed deep within the ASRUL. One was submitted *in toto* for mycobacterial and fungus cultures; Papanicolaou smears were made from the other; all these tests were negative. Although

Figure 2.—A, Admission posteroanterior and **B,** lateral views of the chest in case 1 in April 1975.

fully cooperative, the patient continuously swallowed air throughout bronchoscopy, inducing frequent belching. Some white, frothy gastric juice was twice noted at the mouth in association with these eructations. She remained well at home until the ninth day after bronchoscopy when chills, fever to 38°C (101°F) and a nonproductive cough occurred. On admission to hospital the following day, roentgenograms showed a dense pneumonia confined to the ASRUL (see Figure 4B, C). Blood cultures were negative. Sputum could not be raised initially. Ampicillin therapy, 2 grams per day given intramuscularly, was begun. A "sputum" specimen the following day showed only rare leukocytes and occasional Gram positive cocci in pairs. Culture of this specimen produced light growth of Hemophilus influenzae.

Figure 3.—July 1976 posteroanterior film in case 1 showing 90 percent resolution of previous disease with some residual scarring.

Temperature dropped to normal within 24 hours, but the radiographic density cleared very slowly over 14 days. Osteotomy and bone grafting to the femur was finally done in October 1974. There were no further respiratory problems. Roentgenograms in 1976 showed complete clearing. The nature of the cavitary lesion could never be established. Although aspiration of oropharyngeal and gastric contents and possible exacerbation of a low grade, chronic cavitary anaerobic pneumonitis may be factors, the acute pneumonic process seems clearly related to the local trauma during bronchoscopy.

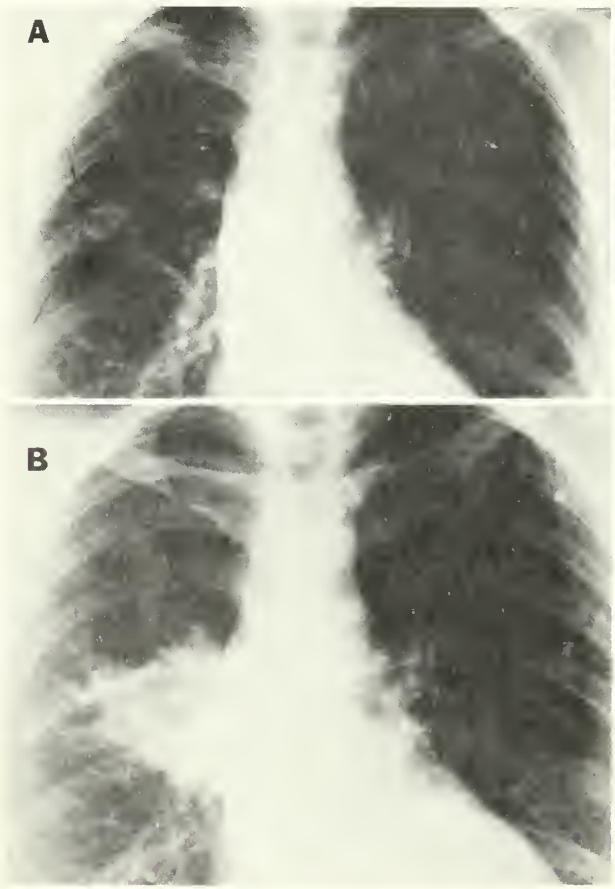

Figure 4.—Case 2. Three roentgenograms: **A,** One from July 1974 which is a representative prebronchoscopic posteroanterior chest film; and **B & C,** two from September which are postbronchoscopic posteroanterior and lateral films showing an anterior segmental pneumonia of the right upper lobe.

CASE 3. A 46-year-old man was admitted to hospital on June 25, 1975, because of a dry hacking cough for two months and intermittent sharp pleuritic chest pains. He had smoked two packs of cigarettes a day for 20 years. Findings on physical examination were normal. An x-ray film of the chest showed two left upper lobe infiltrates and a left hilar mass (see Figure 5A, B). An intermediate purified protein derivative (PPD) skin test was positive but sputum concentrates and cultures were negative for acid-fast bacilli. Spirometry showed normal lung volumes and flow rates, though all measurements improved after bronchodilators. Arterial blood gas studies showed an oxygen tension (Po_2) of 85 torr, carbon dioxide tension of 30 torr and pH of 7.45. On transnasal fiberoptic bronchoscopy on June 26, 1975, 90 percent occlusion of the apical posterior orifice of the left upper lobe (APLUL) was found. Four biopsy specimens taken within the segment were nondiagnostic, but bronchial brushings showed poorly differentiated carcinoma. The pa-

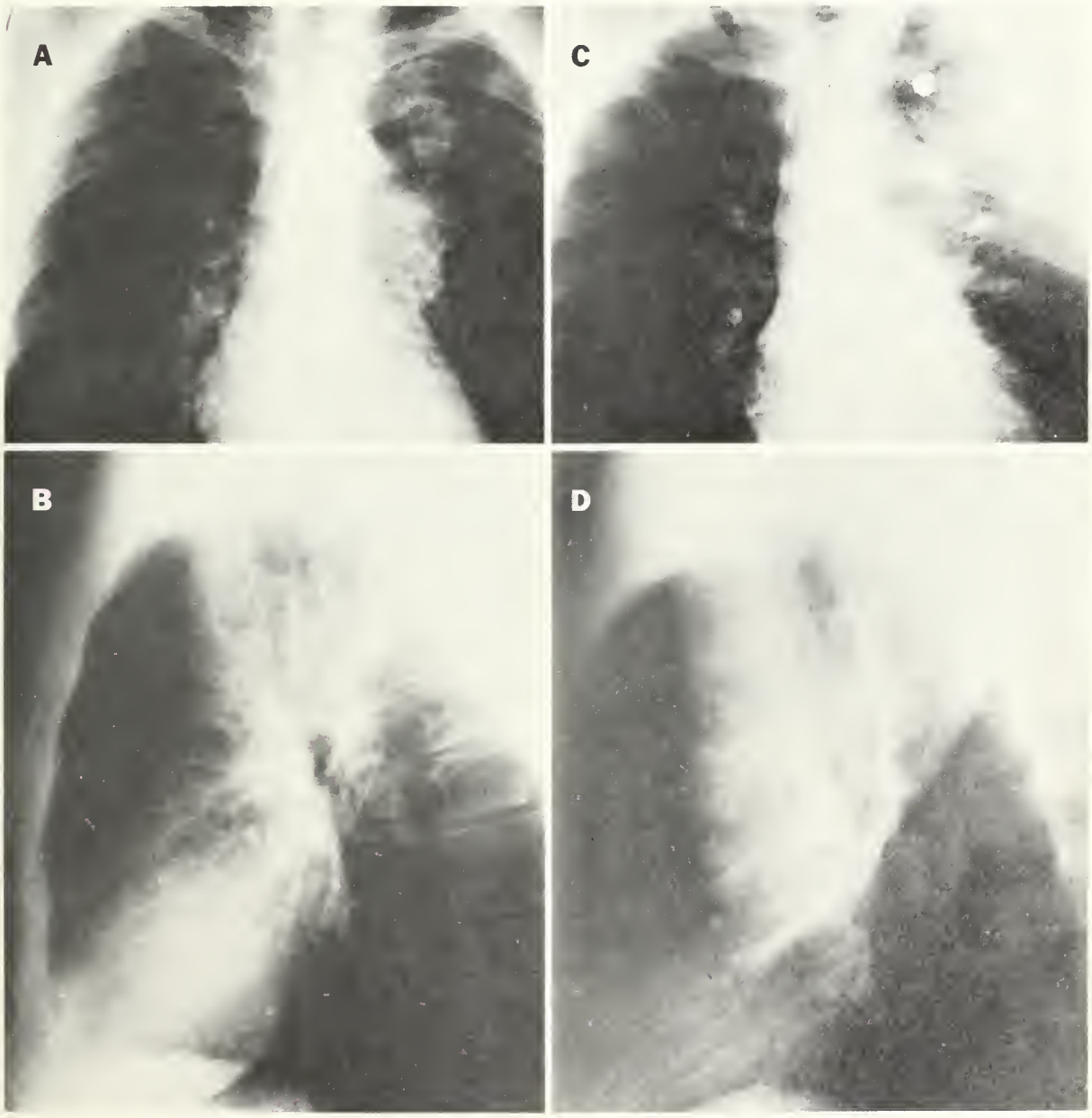

Figure 5.—Posteroanterior and lateral chest films in case 3, **A & B,** before and **C & D,** after bronchoscopy, showing a left upper lobe lesion and subsequently a dense pneumonia localized to the apical posterior segment of the left upper lobe.

tient remained afebrile that same afternoon and the next morning on hospital discharge.

Three days after bronchoscopy, he awoke with a temperature of 39°C (103°F), left anterior chest pain, and a cough productive of large amounts of yellow sputum. On readmission to hospital that evening, temperature was 40.5°C (105°F) and a roentgenogram of the chest showed a dense pneumonia confined to the APLUL. An initial sputum examination (and many subsequent ones over the next six weeks) showed large numbers of leukocytes, many Gram negative rods and heavy growth of Escherichia coli sensitive to ampicillin, cephalosporins, gentamicin and chloramphenicol. Transtracheal aspiration was not done because uncontrollable coughing made the procedure prohibitively risky. Multiple blood cultures were negative. Despite therapy with gentamicin and penicillin, the patient continued to bring up copious amounts of purulent nonputrid sputum for the next six weeks while multiple cavitations developed within the initial density, indicating a necrotizing pneumonia. On cervical node biopsy, oat cell carcinoma was found. When the infection was controlled, chemotherapy with 5 fluorouracil, cytoxan and vincristine (and Laetrile, which his family obtained elsewhere) failed to alter a rapid downhill course with respiratory insufficiency causing death November 7, 1975.

In summary, a necrotizing pneumonia developed in the area of bronchial brushings and biopsy on the third day following bronchoscopic examination and responded very slowly to antibiotic therapy. This was likely a mixed infection involving both E. coli and anaerobes, and it probably responded poorly because of the pronounced bronchial obstruction.

Discussion

Pneumonia following fiberoptic bronchoscopy has been reported rarely.[1,3] In a prospective study[3] of 100 consecutive bronchoscopies, Pereira and co-workers have shown that fever and pulmonary infiltrates frequently occur after the procedure but are *usually* of little consequence. Sackner's comprehensive monograph on fiberoptic bronchoscopy[5] mentions infectious complications only briefly—when reviewing Pereira's study.

The occurrence of these three serious infections within a year at the same facility immediately suggests three possible explanations: (1) these patients were unique, (2) the procedures were somehow carried out in a fashion that predisposed to infection or (3) pneumonia is actually underreported in the medical literature.

We believe the third explanation is most likely correct. The first two explanations appear unlikely as detailed below:

Were Our Patients Unique?

All three patients were smokers. Two had a history of asthma but were free of bronchospasm during the time of observation. Although two of them had apparent chronic infections, neither of these gave a history suggesting increased susceptibility to bacterial infections. Only in case 3 was there an obstruction of a major bronchus. These features do not distinguish our three patients from our other patients in whom fiberoptic bronchoscopy was done. The features also do not confirm Pereira's observation that age over 60, presence of carcinoma and use of brushing techniques predispose to febrile, pulmonary infiltrative reactions. Our patients were relatively young and two of them had benign disease.

Did Our Technique Predispose to Infection?

Our procedure included both transnasal[6] and transoral approaches.[7] The three cases discussed were numbers 60, 100 and 119 of a series of 380 diagnostic bronchoscopies done during a five-year period.[8] This included 41 patients with transbronchial lung biopsies, 212 with endobronchial biopsies and 302 with bronchial brushings. No other serious pulmonary infections occurred and in fact the only other important complications in the series were three minor pneumothoraces after transbronchial biopsy. Could a contaminated bronchoscope have introduced the organisms responsible for these infections? Webb and Val-Spinosa[9] described three cases of pulmonary infections with Serratia marcescens due to a contaminated bronchoscope. This possibility has been ruled out: the bronchoscope is cold sterilized by the manufacturer's recommended technique with 50 percent betadine, 25 percent alcohol solution for 20 minutes just before the procedures. Subsequent contamination by personnel is minimized by use of sterile gowns and gloves.

The effectiveness of these precautions was evaluated following Case 1. During 210 consecutive procedures, the bronchoscope channel was flushed with 10 ml of sterile saline without preservatives just before insertion. These rinsings were submitted for routine, fungal and mycobacterial cultures. Ten of them were submitted in

gassed-out tubes for anaerobic cultures. All cultures were negative except two: one grew seven colonies of Aspergillus species on routine culture; the same specimen showed no growth on a Saboraud medium, suggesting a laboratory contaminant; another grew Hemophilus influenzae. These data provide good evidence that the bronchoscope *is* sterile before introduction into the patient's airway. Presumably the infections were related to seeding of organisms already present in the upper respiratory tract of these patients.

Conclusion

We believe that these three cases illustrate unpreventable pulmonary infections incident to diagnostic fiberoptic bronchoscopy. We suspect that such infections are not as rare as the current medical literature suggests. While precise understanding of the pathogenesis of these infections is wanting, it appears evident that infection is more likely to occur in diseased areas that are further traumatized by biopsy and brushing procedures. These serious infections must be distinguished from self-limited febrile reactions which frequently occur within 24 hours after bronchoscopy. We conclude that any temperature over 38°C (100°F) that occurs after the procedure requires close observation. When clinical assessment and roentgenograms indicate pulmonary infection, appropriate Gram stains and cultures should be done immediately and the patient treated with antimicrobials. Transtracheal aspiration for aerobic and anaerobic culture should be done when feasible. The prolonged course of infection in these cases suggests that rapid treatment is imperative, even though this will undoubtedly include some patients who might otherwise have recovered spontaneously.

Summary

Previous reports indicate that infectious complications of fiberoptic bronchoscopy occur infrequently and usually resolve without specific antimicrobial therapy. This report details three instances of serious pulmonary infections occurring three to nine days after the procedure. Each infection was localized within a segment which was brushed or biopsied during fiberoptic bronchoscopy. These three cases suggest that any fever occurring afterwards requires close scrutiny and prompt treatment with antimicrobial agents when pulmonary infection is present.

REFERENCES

1. Credle WF, Smiddy JF, Elliott RC: Complications of fiberoptic bronchoscopy. Amer Rev Resp Dis 109:67-72, 1974

2. Suratt PM Smiddy JF, Grubert B: Deaths and complications associated with fiberoptic bronchoscopy. Chest 69:747-751, 1976

3. Pereira W, Kovnat DM, Khan MA, et al: Fever and pneumonia after flexible fiberoptic bronchoscopy. Am Rev Resp Dis 112:59-64, 1975

4. Bennett JE: Flucytosine. Ann Intern Med 86:319-322, 1977

5. Sackner MA: State of the art: Bronchofiberoscopy. Am Rev Resp Dis 111:62-88, Jan 1975

6. Smiddy JF: Transnasal fiberoptic bronchoscopy. RI Med J 55:351-352, 1972

7. Ikeda S: Atlas of Flexible Bronchofiberoscopy, Baltimore, Univ Park Press, 1974

8. Aelony Y: Fiberoptic bronchoscopy as an outpatient procedure—Presented at the World Congress on Bronchoscopy, Tokyo, Jul 11, 1978 (Proceedings in press)

9. Webb F, Val-Spinosa A: Outbreak of Serratia marcescens associated with the flexible fiber bronchoscope. Chest 68:703-708, Nov 1975

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

On Smoking and Advertising

To the Editor: Dr. E. R. W. Fox's letter in your June issue (pages 559-560) was slightly off track, if not completely derailed.

The tobacco manufacturers have repeatedly stressed that they do not want or seek young people as customers. Cigarette advertising is a means of maintaining or increasing brand loyalties in an established market of smokers. Its aim and result is not "enticing" new smokers.

HEW's John Pinney, Director of the Office of Smoking and Health, refuted the "sinister advertising" charge when he said, "It is quite correct not to make ads the culprit in terms of why teenagers take up smoking. Advertising certainly is not the culprit."

The tobacco industry's advertising standards are some of the strictest in practice. All models must be 25 years old and look it. There is no advertising, sampling or promotion of cigarettes on any campus in America. No testimonials by athletes or celebrities are used in cigarette advertising.

One fact that is too often forgotten is that the cigarette manufacturers volunteered ten years ago to stop advertising on television and radio, because youth audiences had become too large.

Attempts to tie the teenage smoking problem to anything other than misguided peer pressure are wrong. After all, marijuana use among teenagers has substantially increased, without any advertising.

RICHARD R. MILLER
Director of Media Relations
The Tobacco Institute, Inc.
Washington, DC

* * *

Dr. Fox Replies

To the Editor: Mr. Miller, as Director of Media Relations for the Tobacco Institute, is understandably irritated by my comments in the June issue. I find his arguments unconvincing.

To suggest that magazine and newspaper advertising has no impact on the youth of America goes counter to Madison Avenue experience. The magazines that are most widely seen by young people—ladies' and sports' periodicals—abound with seductive cigarette ads.

The mere fact that the tobacco industry has made some concessions regarding their advertising format means they know that advertising most certainly does influence impressionable youthful minds. The advertising message is clear: Cigarette smoking is glamorous. To smoke is to enjoy gracious living. Smoking is sexy, it lends charisma. These messages produce "peer pressure."

It would be best, of course, if the printed media would voluntarily follow the example of TV and radio. It is noteworthy that two fine magazines, *Sunset* and *Good Housekeeping,* carry no cigarette ads whatsoever.

At the recent meeting of the House of Delegates of the American Medical Association the members sent out this strong directive: "Step up the antismoking campaign."

It looks like we are on the right track after all.

E. R. W. FOX, MD
Special Editor for Idaho
Coeur d'Alene, Idaho

Exercise and Neuromuscular Disease

To the Editor: The provocative title "Hazards of Exercise in Patients with Weakness of Neuromuscular Origin," an Epitome of Progress in the August issue,[1] may be a disservice to those with neuromuscular disease and inadvertently promotes a nihilistic management approach. The origins of potential misinformation are threefold: (1) extrapolation from animal models to man, (2) comparison of normal and *leaky* myopathic muscle and (3) generalizations about neuromuscular disease.

It is inadvisable to compare animal models of murine muscular dystrophy with the varieties of human muscular disease. The maximal exercise situations in experimental trials may have little relevance to a prudent, graded program of physical activity.

In normal human muscle, leakage of creatine phosphokinase (CPK), resulting in increased serum enzyme activity, may signify damage to the muscle plasmalemma. However, in abnormal muscle, such an inference may be unwarranted. For example, in boys with Duchenne muscular dystrophy, major fluctuations in serum CPK activity may occur without physical activity.[2,3] In the presence of extraordinarily permeable muscle membranes, elevation of CPK activity may reflect more an increase in enzyme synthesis than muscle damage. A strengthening muscle program may promote a generalized increase in muscle protein synthesis and secondarily an increase in serum CPK activity. Reliance upon serum CPK in this instance would be misleading.

Finally, while *neuromuscular disease* is a convenient and satisfactorily noncomittal term for abstract purposes, more discriminant terminology is desirable for clinical use. For example, patients with anterior horn cell dysfunction (whether from previous poliovirus infection, chronic neurogenic limb-girdle syndromes, benign focal amyotrophy, or amyotrophic lateral sclerosis) are afflicted with a process entirely different from those with intrinsic muscle cell disease (myopathy). In neurogenic disease, loss of motor units (producing weakness) may be compensable by hypertrophy of surviving units and collaterally reinnervated muscle. Even in patients with myopathy, there is no evidence that a planned program of exercise is harmful, and clinical experience would suggest the contrary.

Frequently, patients who can increase the strength of selected muscle groups by as little as 10 percent may gain a substantial benefit in function. Given the usual lack of enthusiasm for physical therapy and graded muscle strengthening programs by both patients and physicians, it would be more appropriate to caution the hazards of disuse atrophy in patients with neuromuscular disease.

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REFERENCES

1. Taylor RG: The hazards of exercise in patients with weakness of neuromuscular origin (Important Advances in Clinical Medicine—Epitomes of Progress: Physical Medicine and Rehabilitation). West J Med 131:132-133, Aug 1979

2. Adornato BT, Kagen LJ, Engel WK: Myoglobinemia in Duchenne muscular dystrophy patients and carriers. Lancet 2: 499-501, 1978

3. Mendell JR, Engel WK, Derrer EC: Increased plasma enzyme concentrations in rats with functional ischaemia of muscle provide a possible model of Duchenne muscular dystrophy. Nature 239:522-524, 1972

Toxicity of the Herbicide 2,4,5-T

To the Editor: Dr. Sheldon Wagner's letter in the August 1979 issue (page 156) concerning the herbicide 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and its unavoidable and extraordinarily toxic contaminant TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) calls for comment.

I fully agree that physicians should involve themselves in public health issues such as agricultural chemicals. However, these issues are very complex and require a broad perspective with input from a variety of sources and disciplines in addition to medicine.

The United States Environmental Protection Agency (EPA) did not make its decision for an emergency suspension of certain applications of 2,4,5-T solely because of the results of the Oregon study. This information when added to a number of other pieces of accumulating evidence triggered a decision to suspend the use of 2,4,5-T on forest lands and pastures because the spray season was about to start and 7 million pounds were about to be applied. The other pieces of accumulating evidence are substantial. TCDD is the most toxic synthetic chemical known. Animal studies by different investigators in many different animal species, including primates, show it to be carcinogenic and teratogenic, and to cause reproductive abnormalities including birth defects in extremely small doses in the parts per trillion range. Under certain conditions, TCDD is persistent in the environment and has entered food chains. It has been detected in human milk in areas near sprayed forests where aerial application makes drift unavoidable and often extensive. (TCDD is expected to be present in 2,4,5-T at no greater than 0.1 part per million, but ten years ago in Agent Orange, as used in Vietnam, it was present up to 50 ppm.)

Action to cancel uses of 2,4,5-T began in 1970 when its application in lakes and ponds, in recreation areas, around homes and on food crops was suspended. A series of actions and proceedings regarding uses of 2,4,5-T were taken and cancelled during the next few years. This process was hampered by technical difficulties in chemical analysis. The extreme toxicity of TCDD and the

need to detect it in parts per trillion have delayed the development of needed data, particularly food residues and magnification in the food chain, presence in beef fat, human milk, and so forth. These difficulties still persist to a lesser extent.

In 1978 the EPA issued a Rebuttable Presumption Against Registration (RPAR). RPAR is in an in-depth review of the risk/benefit analysis the agency conducts against suspect pesticides. Most of them were introduced many years ago when there were few or no requirements for testing pesticides before registration to determine their adverse effects upon human health or the environment and to develop adequate laboratory analytic methods for that purpose. The RPAR process was well underway with hearings scheduled in late 1979 when the emergency suspension was issued in February 1979. This suspension has successfully held through one administrative and two judicial hearings and has the effect of withholding certain uses of 2,4,5-T until the RPAR hearings produce a final decision.

The Oregon study is a limited but valid epidemiological study demonstrating a statistically significant increase in the spontaneous abortion rate index during 1972-77 among a group of women living in areas where 2,4,5-T was applied by air to forests every spring and sometimes in the fall as well. There was a statistically significant cross-correlation between the spontaneous abortion index and the amount and time of 2,4,5-T applications. The study included two control groups. The health information is based primarily on hospital records. Much of the work was carried out under contract with Colorado State University. There was no claim that the results of this or other epidemiological studies prove cause and effect relationships.

At any rate, the EPA cannot be accused of precipitous action based on one piece of information. It has been curtailing uses of 2,4,5-T, and accumulating considerable information on the subject since it was established in 1971. Further, the absence of reports of *intoxication* in the medical literature does not give a chemical a clean bill of health. Adverse effects can be long delayed and go undetected. Cancer and genetic defects may take years to develop and the cause or causes are more likely to go unrecognized. Other health problems due to exposure to chemicals in the environment, such as reproductive abnormalities, are very difficult to sort out from those due to other and unknown factors. Only under particularly propitious circumstances can the primary tool for detection of relationships between adverse health effects and their potential causes in human population, the epidemiological study, be brought to bear. Waiting for the population to demonstrate the adverse effects on their health from untested chemicals placed in their environment without their knowledge or consent is crassly immoral. This process takes away civil rights from people and gives them to chemicals which are therefore considered innocent until proved guilty, usually by demanding overwhelming evidence reported in the scientific literature. Fortunately, the situation has changed with respect to introduction of new chemicals. They must now present considerable health and environmental impact data before they can be used. It is those chemicals which have been around for several decades, such as 2,4,5-T, which are presenting awkward problems of the type just described.

The California Department of Health Services has issued a policy statement supporting the EPA action, but suggesting EPA may not have gone far enough by excluding rice fields and rangelands from the emergency suspension.

IRMA WEST, MD, MPH, Chief
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State of California Department of Health Services
Sacramento, California

Human Intestinal Parasites in a Farm Community

To THE EDITOR: In an earlier communication, Dr. Ming M. Wong pointed out the need for "medical practitioners in our area [to be alerted] about the prevalence of parasitic diseases they may encounter in their practice[s]"[1] Dr. Wong expressed concern over the "importation of parasite populations (diseases) through the influx of migrant workers and foreign immigrants to the West Coast. . . ."[1] We did a survey for human intestinal parasites in Cantua Creek, a small farm labor community 60 miles southwest of Fresno, California, between April and August of 1975.

Cantua Creek had a population at that time of approximately 1,800 people including Mexican-Americans, Punjabis and Caucasians. The survey was of two camps (134 subjects). Three fecal samples per subject were collected and analyzed

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for ova and parasites by the Ritchie sedimentation technique and direct microscopic observation after staining with 2 percent D'Antoni iodine solution. Specific goals of the survey were (1) to determine parasite prevalence, (2) to determine if parasite transmission was occurring and (3) to correlate demographic information with parasite prevalence.

Figure 1 shows parasite prevalence according to nationality. The Punjabis (8 families, 48 subjects) had the greatest incidence of Entamoeba histolytica, Entamoeba hartmanni, Entamoeba coli, Endolimax nana, Giardia lamblia, Iodamoeba bütschlii and Chilomastix mesnili. They were the only nationality with Ancylostoma duodenale (species determined by hatching ova and observing the larvae). The Mexican-Americans (11 families, 71 subjects) had a prevalence of Hymenolepis nana equivalent to the Punjabis. One incident of infection from the Taenia sp was found in a 13-year-old girl who had come from Mexico within the last few months. The only parasitic infection in a Caucasian (4 families, 13 subjects) was that of G. lamblia in a 7-year-old girl.

Transmission of C. mesnili, E. coli, E. hartmanni, E. histolytica and G. lamblia was probably occurring in Cantua Creek. Six subjects—aged 7 years, 3 years, 2 years, 1 year, 7 months, and 1 month—representing all three nationalities were infected with one or more of these protozoans. None of the subjects had ever lived outside of the United States. Four of the six persons had family members with the same parasitic infection, suggesting an intrafamilial transmission. There were no data suggesting contamination of a common water supply.

In summary, demographic information indicated that the occurrence of a particular parasite infection was correlated more with the nationality of

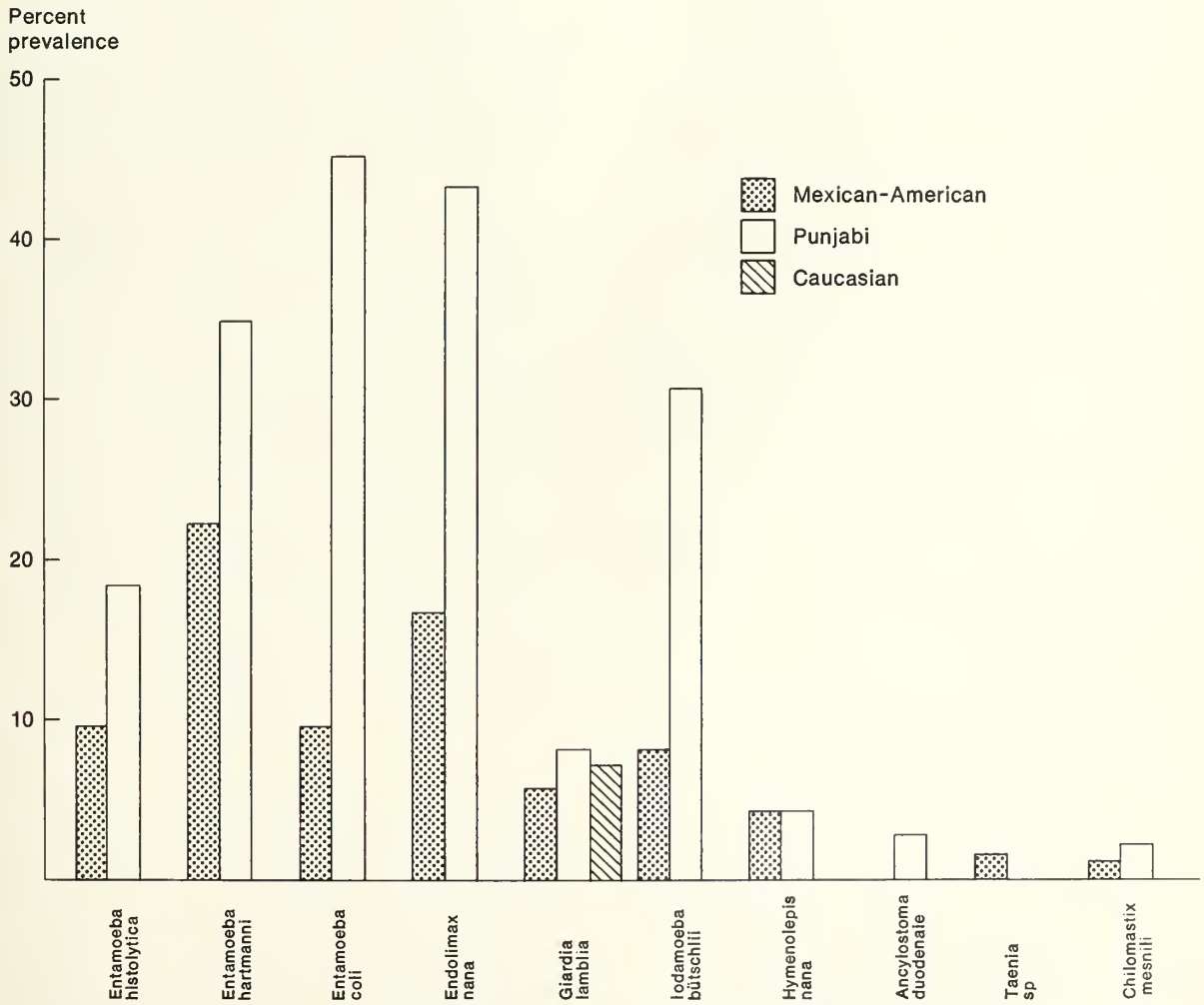

Figure 1.—Percentage of parasite prevalence by ethnic group

the person and where that person had previously lived than with the sex or age. It is appropriate to end this communication, as Dr. Wong ended her comments, by reaffirming the suggestion of Dr. David Sencer (in his delivery of the 33rd Charles Franklin Craig lecture in 1968) that "in this shrinking world one of the first questions that should be asked in taking the medical history is, 'Where have you been?' "[2]

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REFERENCES

1. Wong MM, Karr SL Jr, Lim KC: Parasitic infections among traveling students (Correspondence). West J Med 125:328, Oct 1976
2. Sencer DJ: Health protection in a shrinking world. Am J Trop Med & Hyg 18:341-345, May 1969

Treatment of Gonococcal Pharyngeal Infections in Men

To the Editor: Gonococcal pharyngitis is being recognized as an increasingly common venereal infection. The natural history of the infection is as yet undefined. There is a suggestion in the literature that the gonococcus may exist as a transient pharyngeal colonizer similar to the meningococcus.[1] However, the pharynx may also serve as a locus for dissemination[2] and perhaps as a site for sexual transmission.

Clinicians are faced with the problem of selecting an appropriate therapeutic regimen, unfortunately there are few studies available evaluating the efficacy of current United States Public Health Service (USPHS) recommendations for the treatment of pharyngeal gonorrhea. This study is a retrospective review of our experience in the therapy of 139 cases of gonococcal pharyngitis in men treated according to current USPHS recommendations.[3]

Patients and Methods

The charts of 139 men with gonococcal pharyngitis diagnosed and treated between January 1, 1978, and June 1, 1979, were randomly selected from the clinic files. Only those cases in which a follow-up culture was obtained within 4 to 14 days of completion of therapy were included in the study group. Therapeutic failures were specifically questioned by the examining physician regarding reexposure. Those with a history of reexposure were excluded from the study group.

All pharyngeal cultures were obtained in the recommended manner using a cotton swab,[4] plated immediately on modified Thayer Martin media and incubated in candle jars within ten minutes of collection. Gonococci were identified by oxidase reaction and confirmed by sugar fermentation testing.

A total of 102 patients were treated with 4.8 million units of aqueous procaine penicillin G (APPG) given intramuscularly plus 1 gram of probenicid given orally; 37 received tetracycline, 500 mg orally four times per day for five days.

Results

There were seven failures in 102 patients treated with the APPG regimen (5.9 percent failure rate). No failures were noted in the 37 patients treated with tetracycline.

Comments

In spite of the increasing recognition of gonococcal pharyngeal infections, there is a paucity of therapeutic data to guide clinicians in chosing an antibiotic regimen. Compositing data from the most recent therapy review,[5] which included data from Weisner and co-workers' original review,[6] a total of 55 cases (men and women) were treated with APPG and there were five failures or a 9 percent failure rate. For tetracycline there were five failures in 39 treated cases, a 12.8 percent failure rate.

Our retrospective study is the largest single study in the current literature. A total of 139 cases of pharyngeal gonorrhea in men were reviewed. There were seven failures in 102 (5.9 percent) cases treated with APPG, no failures in 37 patients treated with tetracycline. Both of these regimens appear satisfactory for the treatment of pharyngeal gonorrhea. The high cure rate found with tetracycline suggests its potential use also in APPG treatment failures.

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REFERENCES

1. Wallin J, Siegel MS: Pharyngeal Neisseria gonorrhoeae: Colonizer or pathogen? Br Med J 1:1462-1463, 1979
2. Holmes KH, Counts GW, Beaty HN: Disseminated gonococcal infection. Ann Intern Med 74:979-993, 1971
3. Gonorrhea: CDC recommended treatment schedules, 1979. Morbidity Mortality Weekly Rep 28:13-21, 1979
4. Criteria and Techniques for the Diagnosis of Gonorrhea. US Department of Health, Education, and Welfare, Atlanta, Center for Disease Control Publication
5. Kraus S: Incidence and therapy of gonococcal pharyngitis. Sex Transm Dis 6(Suppl):143-147, 1979
6. Wiesner P, Tronca E, Bonin P, et al: Clinical spectrum of pharyngeal gonococcal infections. N Engl J Med 288:181-185, 1973

Refer to: Ostroy PR: Bacterial meningitis in Washington state (Public Health). West J Med 131:339-343, Oct 1979

Bacterial Meningitis in Washington State

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During 1977 the state of Washington maintained a surveillance system for reporting cases of bacterial meningitis. Hemophilus influenzae meningitis was the most common etiologic agent causing bacterial meningitis. A high incidence rate for H. influenzae meningitis was found among American Indians less than five years ago. A focus of ampicillin-resistant H. influenzae meningitis was found in Pierce County among military dependents or persons who had family members or relatives working or attending school with Fort Lewis Army Base personnel. Although relationships between the individual cases were not *detected, the surveillance system continues to seek some association.*

BEGINNING IN JANUARY 1977 the Association of State and Territorial Epidemiologists (ASTE) began surveillance of bacterial meningitis and meningococcemia in 37 states. Information obtained from this surveillance was used for planning the choice and appropriate use of new polysaccharide vaccines that might be effective in preventing the three most common types of meningitis.

Additionally, surveillance provided information on the distribution and prevalence of ampicillin-resistant strains of Hemophilus influenzae and meningococcal serotypes. This paper describes the results of the surveillance system maintained by the Epidemiology Section of the Department of Social and Health Services of the state of Washington.

Materials and Methods

The Washington State Health Services Division has maintained a reporting system for meningococcal (or *epidemic*) meningitis disease since 1915. The Washington State Reference Laboratory and the King County (Seattle) Laboratory confirm and serogroup all meningococcal isolates. Both laboratories then forward these isolates to the Center for Disease Control for confirmation of identity and serogroup. No other cases of bacterial meningitis have previously been required to be reported to the State Health Services Division.

Beginning in early 1977, in cooperation with the Center for Disease Control and ASTE, The Washington State Epidemiology Office sent letters and copies of the bacterial meningitis case report forms to all county health officers soliciting their assistance in reporting all cases of bacterial meningitis. Six months later a similar letter and reporting forms were sent to all nurse epidemiologists and infection control nurses throughout the state of Washington and to the directors of clinical laboratories doing any bacteriologic work within the state.

In July 1977 a summary of the results of the first six months of surveillance was reported in the *Washington State Communicable Disease Report* reinforcing the reporting of bacterial menin-

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gitis cases. Finally, letters were sent to the medical records department of selected hospitals requesting that all cases of bacterial meningitis with date of onset in 1977 be reported to the State Health Services Division Epidemiology Section.

For the purpose of this study a case of bacterial meningitis was defined as (1) a patient with clinical and laboratory findings consistent with bacterial meningitis who had a positive cerebrospinal fluid cultured for any bacterium and (2) a patient with clinical findings consistent with bacterial meningitis and having a diagnosis of bacterial meningitis made by the primary physician despite a negative cerebrospinal fluid culture.

A case of meningococcemia was defined as a patient with clinical findings consistent with meningococcemia and having three or more of the following: purpura, fever, shock, adrenal hemorrhage and positive blood cultures for Neisseria meningitidis.

For each case of meningitis and meningococcemia a case report form was completed by a nurse epidemiologist, a county health department nurse or the Epidemic Intelligence Service officer. Data requested included address, age, sex, race, type of illness (bacterial meningitis, meningococcemia or both), the specific bacterium, whether the organism was isolated from blood or cerebrospinal fluid (or both), the date of onset of symptoms and the outcome. For those cases of meningitis caused by H. influenzae, the status of ampicillin-sensitivity was also requested.

Before forwarding meningococcal isolates to the Center for Disease Control, the state and King County laboratories carried out antibiotic sensitivity studies to sulfonamides and rifampin using the modification of the Kirby-Bauer disc method on Mueller-Hinton agar.[1] At the Center for Disease Control, final confirmation of identity, serogroup and antibiotic sensitivities using the minimal inhibitory concentration was completed. The State Reference Laboratory also documented and did antibiotic sensitivities on a small number of other bacterial isolates causing bacterial meningitis.

Population data are from the 1977 estimate of the Office of Financial Management of the State of Washington which is based on the 1970 United States census.

Results

Of the 203 cases of bacterial meningitis and meningococcemia reported in Washington in 1977, all but four were in Washington residents. Two cases occurred in visitors from California and two from Alaska. The number of cases of meningitis occurring in Washington residents receiving medical care in other states is unknown and, except for meningococcal disease, they would be unlikely to have been reported. Table 1 shows the number of cases, incidence rate, number of deaths and mortality according to etiologic agent for all ages and for children less than five years. Most reported cases were due to H. influenzae (43.3 percent) followed by meningococcal disease (22.2 percent). The overall case-fatality ratio was 13.3 percent. No time clustering was seen for any of the etiologic agents. Of the 203 cases of bacterial meningitis, 161 (79.3 percent) of the reported cases had positive cerebrospinal fluid cultures of a specific bacterium.

Although the statewide incidence rate of H. influenzae meningitis for all ages was 2.5 per 100,000, Grays Harbor and Pierce Counties had incidence rates of 6.5 and 5.4, respectively. Of the reported cases of H. influenzae meningitis, 60 percent occurred in residents of the contiguous counties of Snohomish, King and Pierce, which

TABLE 1.—*Number of Cases and Deaths, Case-Fatality Ratio (CFR), Incidence and Mortality Due to Bacterial Meningitis Listed by Etiologic Agent in Washington State, 1977*

	All Ages					*Less Than 5 Years*				
	No. Cases	*Incidence Rate**	*No. Deaths*	*Mortality Rate†*	*CFR*	*No. Cases*	*Incidence Rate**	*No. Deaths*	*Mortality Rate†*	*CFR*
Hemophilus influenzae	88	2.5	8	0.21	9.1	79	31.8	6	2.4	7.6
Neisseria meningitidis	45	1.3	1	0.03	2.2	22	8.9	0	0.0	0.0
Streptococcus pneumoniae	24	0.7	10	0.27	41.7	11	4.4	1	0.4	9.1
Group B streptococcus	10	0.3	2	0.05	20.0	9	3.6	2	0.8	22.2
Listeria monocytogenes	6	0.2	0	0.00	0.0	3	1.2	0	0.0	0.0
Miscellaneous	30	0.8	6	0.16	20.0	10	4.0	3	1.2	30.0
TOTAL	203	5.8	27	0.68	13.3	134	54.0	12	4.8	9.0

*Cases per 100,000 population
†Deaths per 100,000 population

form the eastern littoral of Puget Sound. Approximately 50 percent of the state's population reside in these counties. Pierce County, which includes Tacoma, reported 2.4 times the number of H. influenzae meningitis cases and 1.8 times the number of meningococcal disease cases expected if the disease was equally distributed among the state's populace.

Considering all the causes of bacterial meningitis, the highest incidence rate (54 per 100,000) occurred in children less than five years old and was almost eight times the next highest rate of 7 per 100,000 seen in persons 80 to 84 years old.

Table 2 gives the incidence of H. influenzae meningitis, meningococcal disease and all other types of meningitis according to race. American Indians had an H. influenzae meningitis incidence rate of 13.5 per 100,000 which was six times that seen for whites. The difference in the proportion for American Indians and for the rest of the population is highly significant ($X^2 = 15.26$; $p < .001$). Indian children less than five years of age had an H. influenzae meningitis incidence rate of 170 per 100,000.

Table 3 depicts the number of cases, deaths, case-fatality ratio, and age-specific incidence and mortality rates for children less than five years old having meningitis caused by H. influenzae, Streptococcus pneumoniae and N. meningitidis.

Comparison of the number of cases and incidence of H. influenzae meningitis occurring in children less than five years old in the two counties having the largest population (King and Pierce) and the remainder of the state, as well as the incidence rates of ampicillin-resistant H. influenzae isolates, is seen in Table 4. Statewide, 18 percent of the H. influenzae isolates causing meningitis were ampicillin-resistant compared with the 38 percent that were ampicillin-resistant among Pierce County's cases of H. influenzae meningitis. Of all ampicillin-resistant H. influenzae isolates, 64 percent were found in Pierce County while only 22 percent of the nonresistant cases were found there. The difference in these proportions is highly significant ($X^2 = 8.06$; $p < .01$).

In order to confirm that the high proportion of ampicillin-resistant H. influenzae isolates were not laboratory errors, we requested that each of the laboratories reporting ampicillin-resistant strains of H. influenzae during 1977 submit to the State Reference Laboratory subcultures of the next five cerebrospinal fluid or blood isolates of H. influenzae. Only two hospitals supplied at least five isolates while one hospital sent in only

TABLE 2.—*Incidence and Mortality Rate of Bacterial Meningitis by Agent and Race, Washington 1977*

	ETIOLOGIC AGENT								*MORTALITY*	
	Hemophilus influenzae		*Neisseria meningitidis*		*All Others*		*Total*		*Deaths*	
	No.	*Rate**	*No.*	*Rate**	*No.*	*Rate**	*No.*	*Rate**	*No.*	*Rate†*
White	71	2.2	39	1.2	48	1.5	158	4.8	24	0.7
Spanish surname	1	1.1	0	0.0	1	1.1	2	2.2	0	0.0
Black	3	3.4	3	3.4	0	0.0	6	6.8	0	0.0
Asian	0	0.0	2	3.3	0	0.0	2	3.3	1	1.7
American Indian	6	13.5	1	2.3	1	2.3	8	18.1	1	2.3
Unknown	7	0.0	0	0.0	20	0.0	27	0.0	0	0.0
TOTAL	88	2.4	45	1.3	70	2.0	203	5.7	27	0.8

*Cases per 100,000 population
†Deaths per 100,000 population

TABLE 3.—*Number of Cases, Incidence Rate (IR), Deaths, Case-Fatality Ratio (CFR) and Mortality Rate (MR) of Bacterial Meningitis by Etiologic Agent in Children 0-4 Years Old in Washington State, 1977*

	Hemophilus influenzae					*Neisseria meningitidis*					*Streptococcus pneumoniae*				
Age	*Cases*	*IR**	*Deaths*	*CFR*	*MR†*	*Cases*	*IR**	*Deaths*	*CFR*	*MR†*	*Cases*	*IR**	*Deaths*	*CFR*	*MR†*
<1	35	70.4	3	8.6	6.0	12	24.3	0	0	0	8	16.1	1	12.5	2.0
1	28	56.4	1	3.6	2.0	4	8.1	0	0	0	2	4.0	0	0	0
2	12	24.2	1	8.3	2.0	4	8.1	0	0	0	1	2.0	0	0	0
3	2	4.0	1	50.0	2.0	1	2.0	0	0	0	0	0	0	0	0
4	2	4.0	0	0	0	1	2.0	0	0	0	0	0	0	0	0
TOTAL	79	31.8	6	7.6	2.4	22	8.9	0	0	0	11	4.4	1	9.1	0.4

*Cases per 100,000 population
†Deaths per 100,000 population

TABLE 4.—*Number and Incidence of Ampicillin-Resistant Hemophilus influenzae Isolates of Meningitis Cases in Children Less Than Five Years Old in Washington State, 1977*

County	*Number Hemophilus influenzae Isolates*	*Incidence Rate**	*Number Ampicillin-resistant Isolates*	*Incidence Rate**
King	27	33.3	2	2.8
Pierce	24	73.7	9	27.6
All other counties	28	22.3	3	2.1
TOTAL	79	31.8	14	5.6

*Cases per 100,000 population

one isolate. Two hospitals sent no cultures. The Washington State Reference Laboratory agreed with the ampicillin-sensitivity status of all 12 isolates forwarded to it. A third of the isolates were ampicillin-resistant as determined by both the Kirby-Bauer disc and beta-lactamase methods, and all of the resistant strains were from Madigan Army Hospital in Pierce County. In contrast, five (100 percent) of the isolates from Children's Orthopedic Hospital in King County were ampicillin-sensitive.

Of Pierce County's ampicillin-resistant H. influenzae isolates, six (67 percent) occurred in children residing in the extreme southernmost portion of the city of Tacoma, just north of the Fort Lewis Army Base. By contrast, only 37 percent of Pierce County's population resides within the Tacoma city limits. While only two (22 percent) of the ampicillin-resistant H. influenzae meningitis cases were in military dependents, seven (78 percent) had parents or other relatives working, attending school or having other close contact with military personnel at Fort Lewis. No data are available regarding the general Pierce County population's employment relationships with the Fort Lewis Army Base. No day-care center, nursery school, church or other group was involved with more than a solitary case of ampicillin-resistant H. influenzae meningitis.

The age distribution of cases of H. influenzae meningitis within Pierce County is very similar to the distribution of H. influenzae meningitis cases in the remainder of the state. The age distribution of the state of Washington and Pierce County differs only in that Pierce County has a very large male population between 18 and 24 years old due to the presence of the military installations, but no cases of H. influenzae meningitis occurred within this population. The populations are, however, almost identical for the under-5-year age group and the remainder of the population. No clustering by time of the ampicillin-resistant isolates within Pierce County was noted.

The distribution of H. influenzae meningitis within the American Indian population of the state of Washington did not differ from that within the non-Indian population in regard to age or sex, and no clustering by time or place was observed. Each of the six cases in the Indians occurred within a different county, all of the H. influenzae isolates were ampicillin-sensitive[3] and all the children survived.

The largest percentage (48.9 percent) of the meningococcal isolates from cerebrospinal fluid or blood in the state of Washington were of serogroup B. Five (11.1 percent) of all meningococcal isolates from cerebrospinal fluid or blood were serogroup A. Four of those occurred in King County residents; two being persons associated with the skid row population where an outbreak of meningococcal A disease occurred in 1976. The Washington State Reference Laboratory sent 29 blood and cerebrospinal meningococcal isolates to the Center for Disease Control for confirmation and serogrouping; 21 of these have been processed. A total of 18 were confirmed as sulfadiazine-sensitive organisms by the Center for Disease Control and the Reference Laboratory. Three were resistant to sulfadiazine according to both laboratories, although the sensitivities were done by different methods—Kirby-Bauer disc method by the Washington State Reference Laboratory and minimal inhibitory concentration by the Center for Disease Control. All of the meningococcal isolates were sensitive to rifampin as determined using the two studies.

Discussion

The methods used in this surveillance system have resulted in underestimation of the true incidence of all causes of bacterial meningitis within the state of Washington in 1977. Without reviewing all hospital records and death certificates for meningitis cases, complete case ascertainment is not possible; however, our surveillance system was helpful in learning about the distribution and prevalence of the various etiologic agents causing bacterial meningitis and specifically for ampicillin-resistant isolates of H. influenzae. H. influenzae, the most frequent cause of bacterial meningitis, has been previously reported.[2-4] It has also been reported previously[5] that there has been an increased incidence of H. influenzae meningitis over

the past few decades but, because this disease has never been reported in the state of Washington, an increased incidence rate is impossible to document. The statewide incidence rate for H. influenzae meningitis was 2.5 per 100,000 and in children less than five was 31.8 per 100,000, but other studies have reported high incidence rates.[3,4,6-8] Even Pierce County's incidence rate of 73.7 per 100,000 for children less than five years old does not approach the highest incidence rates previously reported.[2,4,8] Similarly, Washington's incidence rate of meningococcal disease is lower than in two reported studies[4,7] but the same or higher than in others.[3,8] The incidence rate for S. pneumoniae and meningitis is lower than rates given in those same studies.[3,4,7,8] More comprehensive case ascertainment would likely raise the incidence rate to comparable levels seen in some of these studies.

There was a reporting bias in our surveillance system, due to the excellent cooperation of the Pierce County Health Department and the Madigan Army Hospital Epidemiology Section, that caused a disproportion in number of cases reported from Pierce County, although the high proportion of ampicillin-resistant strains of H. influenzae would not have been preferentially reported.

The high incidence rate of 13.5 per 100,000 for H. influenzae meningitis seen in the American Indian population is similar to the 17.7 per 100,000 rate reported by Coulehan and co-workers.[4] Likewise, the incidence (170 per 100,000) rate for Indian children less than five years of age is almost identical to Coulehan's experience with the Navajos,[4] but much less than reported by Gilsdorf[2] in southwestern Alaska.

The reason for the high incidence of H. influenzae meningitis among the Indian population is unknown. Socioeconomic factors have not been clearly elucidated, but some studies have shown correlation between family income or educational level and frequency of bacterial meningitis, especially that due to H. influenzae and S. pneumoniae.[3,6] No data regarding income or educational level on the Indian or any other population were obtained with this surveillance system.

A focus of ampicillin-resistant H. influenzae isolates was noted within Pierce County and, more specifically, the area adjacent to the northern border of the Fort Lewis Army Base. It was not possible to detect any relationship between cases but, as they continue to occur, enhanced surveillance should, it is hoped, discover any relationship among cases of meningitis caused by these resistant organisms.

Although the total number of meningococcal isolates from blood or cerebrospinal fluid in 1977 was higher than in the past six years, the number of group A isolates was the same as in 1976. In that year a group A meningococcal outbreak occurred in King County where five group A meningococcal isolates from blood or cerebrospinal fluid were cultured from Seattle's skid row population. In 1977, three of the five group A meningococcal isolates occurred in Seattle residents, two of whom had contact with the skid row area.

REFERENCES

1. Bennett JV, Camp HM, Eickhoff TC: Rapid sulfonamide disc sensitivity test for meningococci. Appl Microbiol 16:1056-1060, Jul 1968

2. Gilsdorf J: Bacterial meningitis in southwestern Alaska. Am J Epidemiol 106:388-391, 1977

3. Fraser DW, Gile CC, Feldman RA: Bacterial meningitis in Bernalillo County, New Mexico: A comparison with three other American populations. Am J Epidemiol 100:29-34, 1974

4. Coulehan JL, Michaels RH, Williams CE, et al: Bacterial meningitis in Navajo Indians. Public Health Rec 91:464-468, Sep-Oct 1976

5. Smith E, Hanes R: Changing incidence of *Haemophilus influenzae* meningitis. Pediatrics 50:723, 1972

6. Fraser DW, Darby CP, Koehler RB, et al: Epidemiology of *Haemophilus influenzae* meningitis, *In* Sell SHW, Carzone ET (Eds): Haemophilus influenzae. Nashville, Tennessee, Vanderbilt University Press, 1973, pp 231-239

7. Floyd RF, Federspeill CF, Schafner MW: Bacterial meningitis in urban and rural Tennessee. Am J Epidemiol 99:395-407, 1974

8. Fraser DW, Henke CE, Feldman RA: Changing patterns of bacterial meningitis in Olmstead County, Minnesota 1936-1970. J Infect Dis 123:300-307, 1973

Refer to: Hahn RG, Hutchinson JC, Conte JE Jr: Cardiopulmonary resuscitation in a university hospital—An analysis of survival and cost (Health Care Delivery). West J Med 131:344-348, Oct 1979

Cardiopulmonary Resuscitation in a University Hospital

An Analysis of Survival and Cost

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A cost analysis and study were done of patient survival after inhospital cardiopulmonary resuscitation during one year at a university hospital. The immediate survival rate in 128 patients was 52 percent. Survival to discharge and six-month survival rates were 19 percent and 15.6 percent, respectively. In all, 23 patients (18 percent) had multiple arrests (two to four per patient) during the same hospital stay. Immediate and six-month survival rates in this group were 52 percent (12 patients) and 9 percent (two patients), respectively. Gender or location where cardiopulmonary arrests occurred in the hospital did not influence survival. The cost of a Code Blue (direct expenses only) was $366. We conclude that the outcome following resuscitation at this university hospital compares favorably with the experience of others, and that the direct cost is modest in relation to the results obtained.

EFFECTIVE CARDIOPULMONARY RESUSCITATION (CPR) has been of particular concern in university teaching hospitals because the *Code Blue* (CB) team members change frequently and consist of house staff at different training levels. Patients with multisystem disease who require specialized medical care further complicate this situation.

Studies of survival of patients who underwent CPR for cardiopulmonary arrest (CPA) occurring before admittance to hospital have been published[1,2] with follow-up of six months and longer.[3] Follow-up beyond two months[4] of patients surviving inhospital CPA has not been reported since the early study of Lemire and Johnson.[5]

Although the immediate survival rate following CPR was reported 17 years ago by members of the staff at this institution,[6,7] no systematic evaluation of cost and longer-term survival has ever been undertaken.

Coskey recently reviewed the favorable experience with CPR in a community hospital. The purpose of this study was to assess the overall effectiveness of CPR at a large university hospital.

Methods

The patients at this institution are referred by physicians and clinics serving our metropolitan

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ABBREVIATIONS USED IN TEXT

CB = Code Blue
CPA = cardiopulmonary arrest
CPR = cardiopulmonary resuscitation

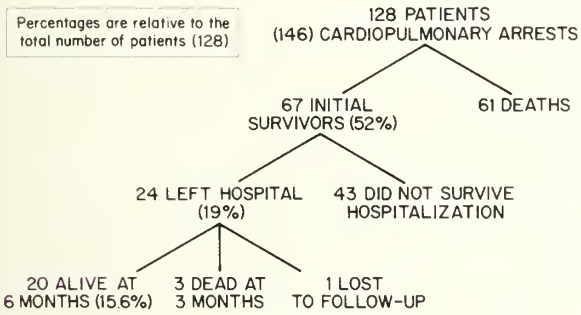

Figure 1.—Survival following cardiopulmonary arrests.

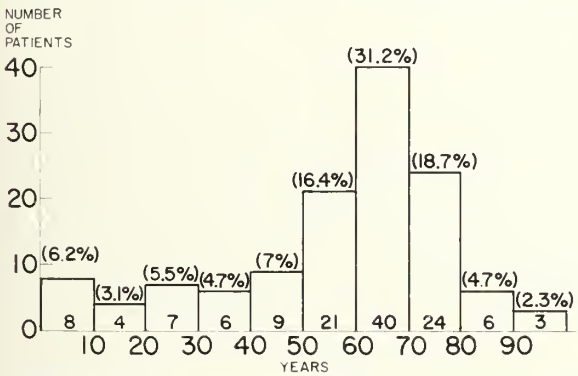

Figure 2.—Age distribution of patients suffering cardiopulmonary arrests.

area and state. The hospital has 560 inpatient beds.

The CB team consists of a medical, a surgical and an anesthesiology resident; a respiratory therapist; a pharmacist; a nurse, and a pediatric resident when necessary. All members carry voice-page beepers which are simultaneously triggered by the telephone operator when a CB is reported. Formal training and certification in CPR were introduced as mandatory requirements in this hospital at the end of 1977. Therefore, the CPR experience of the residents involved with the CB team during this study is indeterminate and probably variable.

Patients were identified through CB report forms completed by the medical resident on the CB team. The locations and times of the events were obtained through the page operator and each CB counterchecked from the reports. The authenticity

TABLE 1.—*Patient Survival by Gender*

	Men		*Women*	
	Number	*(Percent)*	*Number*	*(Percent)*
Immediate survivors	32	(48)	35	(56)
Deaths	34	(52)	27	(44)
TOTAL	66		62	

Chi square = 0.81
P = 0.37

TABLE 2.—*Patient Survival by Service*

	Surgical Service		*Medical Service*	
	Number	*(Percent)*	*Number*	*(Percent)*
Immediate survivors	10	(31)	57	(59)
Deaths	22	(69)	39	(41)
TOTAL	32		96	

Chi square = 7.61
P = <0.01

of each cardiopulmonary arrest was verified by both CB report and chart review.

Arrests were not included in this study if a CB report was not completed or if the telephone operator was not notified. CB patients were excluded from the analysis if they did not have documented evidence of CPA as defined by Jude, Kouwenhoven and Knickerbocker.[8] During the time of the study, the University of California had a *no code policy* for certain categories of patients. No patient in this study fell into the *no code* group.

Follow-up of patients was done by reviewing the charts of those patients remaining within the university clinic system and by telephone contact with the referring physicians for those patients referred to the University.

A patient was considered a survivor at follow-up if his or her levels of consciousness and physical activity were similar to those before admittance to hospital. Patients in whom arrest occurred before arrival at the hospital were excluded from the study. All the Emergency Department CPR's included in the study were de novo arrests occurring while the patients were in that department.

Results

During 1977, there were 147 CB's involving 129 patients at this institution. This number has remained relatively constant during the last three years, when between 130 and 135 CB's per year have been reported. One CB called was not considered to have been a CPA and was therefore eliminated from the analysis. In 23 patients (18

TABLE 3.—*Immediate Patient Survival by Month*

Month	Number of Patients	Number of Code Blues	Immediate Survivors Number	(Percent)
January	11	11	4	(36)
February	9	12	3	(33)
March	11	13	8	(73)
April	9	9	5	(56)
May	11	12	5	(45)
June	9	9	6	(67)
July	14	19	3	(21)
August	11	13	8	(73)
September	12	14	8	(67)
October	6	6	1	(17)
November	15	16	10	(67)
December	10	12	6	(60)

TABLE 4.—*Distribution of Cardiopulmonary Arrests by Location*

Location	Number	Percent
Intensive care unit	33	26
Cardiac care unit	15	12
Emergency department	9	7
Hospital floors	57	44
Others	14	11

TABLE 5.—*Immediate Survival of Patients by Location*

Location	Number/Total	Percent
Intensive care unit	19/33	58
Cardiac care unit	7/15	47
Emergency department	5/9	56
X-ray department	4/5	80
Hospital floors	32/57	56
Miscellaneous areas	4/9	44

percent), more than one arrest occurred, with a maximum of four arrests. All multiple arrests occurred during the same hospital stay, generally within the same 24-hour period. Of the 23 patients with multiple arrests, 12 (52 percent) survived. Two are alive at six months' follow-up (8.6 percent).

Of the 128 patients (Figure 1), 67 (52 percent) survived. Of these survivors, 24 (19 percent) were discharged from the hospital functioning at the same level of activity as before CPA. One patient was lost to follow-up. Three patients died after three months, and 20 (15.6 percent) were alive six months after CPA. Of these 20 patients, five have survived 15 months after arrest, eight have survived 9 months and seven have survived 6 months.

Age distribution of patients is shown in Figure 2. Modal age of the group was 60 to 69 years, and 66.4 percent of the patients were 50 to 80 years old. Sex distribution is shown in Table 1. No relationship between survival and gender was noted. Of the patients, 75 percent were on the Medical Service and 25 percent on the Surgical Service. Of the 20 survivors at six months, 2 were surgical patients, and 18 were medical. Among surgical patients, the immediate survival rate was 31 percent, whereas in the medical group it was 59 percent (Table 2).

Of the CB's, 48 (38 percent) occurred in either

TABLE 6.—*Code Blue Costs**

Equipment		
Monitor and defibrillator $3,500 × 40 units	= $140,000	
Portable suction $161 × 40 units	= 6,400	
Crash cart $650 × 40 units	= 26,000	
	$172,440	$34,488†
Code Blue Committee (yearly)		
Ten members—two hours per month × 12 at $20 per hour	= $ 4,800	
Secretarial time—100 hours × $6.50 per hour	= 650	
	$ 5,450	$ 5,450
Variable Charges		
Drugs	$ 50.00	
Ancillary floor charges	20.00	
Physicians' and nurses' labor‡		
MD's—$9.40 per hour (three house staff)	14.10	
RN's—$8.50 per hour (two nurses)	8.50	
	$ 92.60 × 146	$13,520
Total direct costs	=	$53,458
Cost per Code Blue	=	$ 366

*Excludes any training.
†Five year depreciation.
‡Rates based on a 30-minute resuscitation effort.

the Intensive Care Unit (ICU) or the Cardiac Care Unit (CCU). The immediate survival rate of patients was 56 percent and the six-month survival rate was 8 percent. Distribution of CB's and immediate survival by month is shown in Table 3. Distribution of CB's by location is summarized in Table 4 and immediate survival by location is shown in Table 5. No significant differences were noted, even when widely separated locations were compared.

We were unable to determine CB team response time, but a survey of the nursing staff failed to show any instances where the CB team had been delayed. CPR was routinely started by the ward staff before the team's arrival, which may have contributed to the favorable outcome of the resuscitation. Any criticisms that resulted generally related to the overabundance of medical staff whose presence often hindered the efforts of the CB team.

Cost Analysis

The cost analysis was based on current replacement costs for equipment used in CPR, CB Committee time and other variable charges as summarized in Table 6. Our variable charge was based on a 30-minute resuscitation effort which represents the average for most cases in our study and others. Our direct cost per CPR is $366.

We contacted various general hospitals in the area to determine what charges if any were ever billed in the event of a CPR. Five of the hospitals that answered had no such charge. One charged $40, another charged $98 in the Emergency Department and $124 in the hospital; yet another charged $85. Our hospital had a $120 charge for the Emergency Department only.

Discussion

This study's findings should allay apprehensions of house staff and attending staff regarding the performance of the CB team. Their effectiveness is substantiated by a success rate greater than 50 percent that was documented regardless of whether the arrest occurred in a CCU-ICU setting or elsewhere in the hospital.

Resuscitative efforts are usually more aggressive in teaching hospitals. In view of this fact, the discharge rate from this hospital (19 percent) and six-month survival rate (15 percent) are surprisingly high. Earlier studies have given discharge rates between 8 percent and 25 percent[1,5,9-12] in university hospitals. More recent studies have reported much lower rates (3 percent to 5 percent).[4,13] Community hospital studies uniformly have reported a higher immediate survival and hospital discharge rate (15 percent to 30 percent).[14-19]

The favorable results reported by community hospitals may be attributed to increased selectivity in resuscitative efforts by physicians more familiar with patients' situations and to the complexity of illness in university hospital patients. Our initial survival rate is similar to reported rates for the last 18 years.[1,5,9-12] A three-year follow-up of patients in the 1960's showed a significantly lower death rate beyond six months and an almost static death curve beyond one year.[5] One community hospital study reported 89 percent survival 9 to 42 months postarrest.[16]

As reported in previous studies, ventricular standstill is associated with the poorest prognosis (no survivors out of seven cases).[11] Patients with preexisting chronic obstructive lung disease are also in a poor prognostic category;[11] one of four patients in this category survived in this series.

Most of the surgical patients were in hospital after either open-heart or intra-abdominal operations, whereas the medical patients represented a wide spectrum of disease. We are unable to explain the statistically significant difference in immediate survival between surgical and medical patients; previous studies shed little light on this observation.[9] Almost certainly, underlying disease is an important factor; however, further investigation is necessary to define the determinants of survival after CPA. It is of interest that most studies report very similar short-term and long-term survival rates when comparing cardiac patients with or without acute myocardial infarction with other types of medical and surgical patients undergoing CPR.[9-11,20]

Our only criticism concerns poor record-keeping of CB events, which makes data retrieval extremely difficult. A detailed form and plan for data retrieval has been devised by Peschin and Coakley.[13] Implementation of such a plan requires a firm commitment from all members of the Code Blue team.

Most hospitals, including the University of California, San Francisco, do not charge for CPR. This may be due to the sensitivity of the issue and the difficulty of identifying the cost of resuscitations. The data presented here may serve as a guideline for instituting such a charge.

The CB team's performance should be periodi-

cally monitored to insure continued effectiveness, even though we were unable to detect any differences during the year attributable to level of training.

We conclude that this university hospital's experience with cardiopulmonary resuscitation compares favorably with other institutions.

REFERENCES

1. Eliastam M, Duralde T, Schwartz F, et al: Cardiac arrest in the Emergency Medical Service system: Guidelines for resuscitation. JACEP 6:525-529, 1977

2. Baum RS, Alvarez II III, Cobb LS: Survival after resuscitation from out-of-hospital ventricular fibrillation. Circulation 50: 1231-1234, 1975

3. Lewis AJ, Bebout C, Ailshie GE: Long-term survival fibrillation, abstracted. Circulation 46(supplement 2):60, 1972

4. Messert B, Quaglieri CE: Cardiopulmonary resuscitation: Perspectives and problems. Lancet 2:410-411, 1976

5. Lemire JG, Johnson AL: Is cardiac resuscitation worthwhile?—A decade of experience. N Engl J Med 286:970-972, 1972

6. Rivkin LM, Roe BB, Gardner RE: Cardiac resuscitation through the intact chest. Calif Med 96:75-79, 1962

7. Rivkin LM, Roe BB, Gardner RE: Closed chest cardiac resuscitation. Am J Surg 104:283-291, 1962

8. Jude JR, Kouwenhoven WB, Knickerbocker GG: External cardiac resuscitation. Monogr Surg Sci 1:59-117, 1964

9. Wildsmith JAW, Dennyson WG, Myers KW: Results of resuscitation following cardiac arrest—A review from a major teaching hospital. Br J Anaesth 44:717-719, 1972

10. Kennelly BM: Analysis of a 2 year-old resuscitation service. Resuscitation 3:229-239, 1974

11. Castagna J, Weil MH, Shubin H: Factors determining survival in patients with cardiac arrest. Chest 65:527-529, 1974

12. Jung MA, Selby A, Johnson JR, et al: Value of a cardiac arrest team in a university hospital: Results in a series of 100 patients. Canad Med Assoc J 98:74-78, 1968

13. Peschin A, Coakley CS: A five-year review of 734 cardiopulmonary arrests. South Med J 63:506-510, 1970

14. Dykema ML, Vasu CM: Cardiopulmonary resuscitation in a community hospital—A one-year experience. Mich Med 72:469-472, 1973

15. Beaven WE: External cardiac resuscitation—Experience in a community hospital emergency department. NY State J Med 73: 1810-1814, 1973

16. Jeresaty RM, Godar TJ, Liss JP: External cardiac resuscitation in a community hospital—A three-year experience. Arch Intern Med 124:588-592, 1969

17. Coskey RL: A resuscitation program in a community hospital—Five-year experience. Geriatrics 26:66-72, 1971

18. Polta TA: Cardiopulmonary resuscitation at McKennon Hospital. South Dakota J Med 26:38-43, May 1973

19. Kaunitz VH, Trivedi JM: Cardiopulmonary resuscitation in community hospital. NY State J Med 72:2751-2752, 1972

20. Coskey RL: Cardiopulmonary resuscitation: Impact on hospital mortality—A ten-year study (Health Care Delivery). West J Med 129:511-517, Dec 1978

Refer to: Jacobson JA: Shigellosis in adults—Diagnostic difficulties and delays (Information). West J Med 131:349-351, Oct 1979

Information

Shigellosis in Adults

Diagnostic Difficulties and Delays

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DIARRHEA IN ADULTS is so common[1] and so often self-limited that physicians frequently elect to manage the problem symptomatically. When they do choose to seek an infectious cause, their efforts are usually unsuccessful because Salmonella and, particularly, Shigella infections of otherwise healthy adults in the United States are uncommon (fewer than 9 per 100,000 per year)[2] and other agents responsible for diarrhea, such as enteropathogenic Escherichia coli and several viruses,[3] are not identified by the standard laboratory tests for enteric pathogens. Diarrhea occurring in certain circumstances, however, should arouse suspicion of a bacterial cause, particularly Shigella. These include travel to underdeveloped countries, exposure to facilities where good hygiene is difficult to maintain (such as institutions for the mentally retarded or day-care nurseries), close contact with a recognized case or use of a nonchlorinated, semipublic water system. When these clues are either absent or not elicited, shigellosis is often not considered early as a diagnostic possibility.

The recent recognition of a cluster of three adult patients with shigellosis at our hospital led both our nurse epidemiologist and clinical microbiology staff to bring the cases to our attention. With the public health department, we conducted an epidemiologic investigation which disclosed a previously unrecognized common exposure for two of the cases, but no evidence of a continuing common source epidemic.

Examination of the patients and review of their records showed some of the problems that may arise when this diagnosis is delayed.

CASE 1. A 21-year-old previously healthy woman was admitted on February 20 with the chief complaint of cramping abdominal pain. For two days before admission the pain had been accompanied by nausea, vomiting, watery brown diarrhea, chills and fever as high as 40.5°C (104.9°F). The patient acknowledged orthostatic light-headedness and reported taking a single dose of paregoric without benefit. On physical examination temperature was 37.7°C (99.9°F); pulse, 120 per minute, and blood pressure, 80/50 mm of mercury without postural change. The abdomen had active bowel sounds and was slightly tender without localization or rebound tenderness. Stool guaiac test was negative. Leukocyte count was 2,800 with 13 percent bands, 47 percent polymorphonuclear cells, 37 percent lymphocytes, 2 percent monocytes and 1 percent eosinophils. Serum electrolytes were normal with the exception of the serum sodium which was 129 mEq per liter. The provisional diagnosis was viral gastroenteritis, and fluid and electrolyte replacement was begun. A stool sample was sent for bacterial culture.

On the third hospital day a Gram stain of stool showed one to three leukocytes per high-power field. Although results of the first culture were negative for enteric pathogens, another stool specimen was sent for culture on this day. On the fourth hospital day a stool guaiac test was trace positive. On the fifth hospital day, the labratory reported that the second stool specimen was positive for Shigella flexneri. The patient was then treated with ampicillin, given intravenously and, later, orally in a dosage of 500 mg every six hours for five days. The diarrhea, nausea and vomiting resolved and the patient was discharged on the seventh hospital day.

CASE 2. A 48-year-old woman, the wife of a physician, was admitted on February 21, with a five-day history of fever, diarrhea and abdominal pain. Her illness began with acute onset of chills, fever, vomiting, and watery "red-brown" diarrhea. Because of an episode of near syncope, her husband administered fluids intravenously at home. Three days before admission the patient's husband began treating her with a medication combining diphenoxylate hydrochloride with atropine sulfate (Lomotil, Colonil) and the following day, when little improvement was noted, he obtained a stool specimen for culture and started ampicillin administration.

On admission, the patient had a temperature of

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39.8°C (103.6°F), pulse of 80 per minute, and blood pressure of 104/60 mm of mercury without postural change. Abdominal examination showed only diffuse tenderness without rebound. Stool was guaiac positive. The leukocyte count was 4,000 with 34 percent bands, 36 percent polymorphonuclear cells, 23 percent lymphocytes and 6 percent monocytes. The hematocrit reading was 32 percent, but not greatly different from a result obtained before her illness. The results of stool culture, available on the day of admission, showed Shigella flexneri. The patient was treated with ampicillin, 1 gram given orally every six hours for five days. Fever rapidly resolved, there was gradual improvement of diarrhea and the patient was discharged on the fifth hospital day.

Case 3. An 80-year-old man was admitted to hospital on February 19 because of a three-day history of fever, chills, difficulty with balance, and somnolence. His wife stated that he was also having unusually frequent bowel movements. Past medical history included chronic obstructive lung disease and asthma. On physical examination temperature was 39°C (102.2°F); pulse, 92 per minute; blood pressure, 100/70 mm of mercury supine and 85/65 mm of mercury sitting. Positive findings were limited to the abdomen: there was a pulsatile mass 8 to 10 cm wide in the midline. The patient was incontinent of stool which was of loose consistency and guaiac positive. Pertinent laboratory data included a hematocrit reading of 55.5 percent and a leukocyte count of 11,700 with 23 percent bands, 62 percent polymorphonuclear cells and 15 percent lymphocytes. The blood urea nitrogen was 44 and serum creatinine was 1.5 mg per dl. The results of the lumbar puncture were normal. A stool specimen was sent for culture.

Because of the prominent aortic aneurysm and because the patient (from whom it was difficult to get a good history) gave little emphasis to his symptom of diarrhea, the diagnosis given major consideration was dissecting aortic aneurysm with intestinal ischemia and bacteremia. Nafcillin and gentamicin therapy was instituted. Ultrasonography and angiography confirmed the presence of an 11 by 16 cm abdominal aortic aneurysm. The abdominal great vessels were patent and no bleeding was evident. Because of persistent fever, guaiac-positive diarrhea and the development of abdominal pain, surgical consultants recommended abdominal exploration with the intention of repairing the aneurysm which was felt to be contributing to or causing the patient's illness. At operation, on the patient's third hospital day, an intact aortic aneurysm was removed and replaced with a prosthetic graft. No signs of bleeding or bowel ischemia were seen. The colon was noted to be erythematous, suggesting an inflammatory colitis. On the fourth hospital day the laboratory reported that stool cultures were growing Shigella flexneri. Administration of ampicillin, 1 gram intravenously every six hours, was begun and continued for five days. The patient's fever and diarrhea resolved and cultures of stool specimens obtained during and after therapy were negative for Shigella. The patient's postoperative course was uncomplicated and he was discharged on the 17th hospital day.

The Shigella strains isolated from this patient and from the other two patients were sensitive to ampicillin, cephalosporins, chloramphenicol and tetracycline by Kirby-Bauer disc susceptibility tests.

Discussion

These cases illustrate several points that should be emphasized in the diagnosis and management of acute infectious diarrhea.

First, a careful history with emphasis on significant exposures is essential. Contact with similarly affected persons, particularly young children, should arouse suspicion of an infectious cause, especially Shigella. Recent foreign travel and exposure to crowded institutions should be discussed. Swimming in contaminated rivers is another recently recognized risk factor.[4] Inquiry should be made about water supply, recent food purchases and meals eaten at home or in restaurants. While most outbreaks result from spread from person to person, water and food, especially salads, have been implicated in sporadic cases and common source epidemics.[5] Interviews with our patients disclosed that two of them had eaten at the same restaurant 48 hours before onset of their illnesses. Both had eaten salads, which their unaffected dinner partners had not. The third patient had also dined out, an unusual event for him, two days before his illness and had eaten salad with his dinner.

Second, distinguishing shigellosis clinically from viral gastroenteritis is not always easy because of the wide variation in severity seen with both syndromes. However, fever, abdominal pain

and diarrhea with blood or pus in the stool should heighten one's suspicion of shigellosis.

Third, because patients' observations are unreliable predictors of the presence of red blood cells or leukocytes in their stool, a guaiac test and microscopic examination of stool should be done in all cases where diarrhea is an acute and clinically significant problem. Fecal leukocytes are seen with regularity in symptomatic shigellosis and their presence, though not entirely specific, should suggest an invasive process which is not characteristic of toxigenic or nonbacterial gastroenteritis.[6] Blood in the stool is detected in up to 50 percent of patients with shigellosis and may occur intermittently, as in case 1. Blood in the stool is not characteristic of viral gastroenteritis. Culture of freshly passed stool is the only way to make the diagnosis of shigellosis and several specimens should be submitted to increase the likelihood of a positive culture.[7] Not all specimens will be positive, as indicated by case 1.

Fourth, in managing patients with diarrhea, drugs that interfere with intestinal motility probably should be avoided unless clinical or laboratory evidence weighs heavily against infection. It has been postulated that the hypermotility that accompanies infectious diarrhea is actually a salutary process which hastens recovery from these usually short, self-limited infections. DuPont and Hornick[8] have shown that in shigellosis the diphenoxylate hydrochloride with atropine sulfate medication actually prolonged the duration of diarrhea in patients treated with an antibiotic. In patients who received no antibiotic, the medication shortened the duration of diarrhea but fever persisted two to three times longer than in those who did not receive the drug. It is possible, therefore, that in case 2 fever or diarrhea, or both, may have been prolonged by this therapy.

The use of antibiotics in severe shigellosis is desirable and they appear to shorten[9] rather than prolong the carrier state, as they do in salmonellosis.[10] The choice of antibiotic depends in part on the species and antimicrobial susceptibilities of the strain isolated but the most frequent species isolated from endemic cases in the United States, Shigella sonnei, is generally susceptible to trimethoprim/sulfamethoxazole as is Shigella flexneri. The latter is also usually susceptible to ampicillin.[11]

Properly constituted therapy with orally given fluids can ameliorate the symptoms of fluid loss and electrolyte imbalance that accompany acute infectious diarrhea. While most useful for toxigenic types of diarrhea, such therapy may make a critical difference in the need for hospital versus home management of patients with shigellosis.[12]

The diagnosis of shigellosis was ultimately established in the three cases described, but only after expensive hospital stays and, in one case, major abdominal operation. Admission to hospital may have been necessary for each of the patients because of the severity of their symptoms, but conceivably it could have been avoided or shortened by an earlier diagnosis. A rapid diagnostic test for shigellosis would be a welcome way of avoiding these problems, but until one is available, the diagnosis in sporadic cases depends on a careful history and physical examination and appropriate laboratory tests of stool specimens, and on the physician's perspicacity. An algorithm for the diagnosis of acute diarrhea has been published and may serve as a useful guide for physicians who see patients with this problem.[13]

The difficulty of diagnosing shigellosis in adults is not a new problem and has been discussed previously in a report that noted that in only nine of 30 patients was the disease diagnosed correctly on admission.[14] In that study, fever was present in 77 percent, blood in stool in 50 percent and a shift to the left in the differential leukocyte count in 100 percent. These findings in patients with diarrhea plus a positive methylene blue stain for fecal leukocytes suggest that shigellosis should rank quite high on a list of possible diagnoses.

REFERENCES

1. Johnson AC, Kroeger HH, Altman I, et al: The office practice of internists—III. Characteristics of patients. JAMA 193: 916-922, Sep 1965

2. Rosenberg ML, Weissman JB, Gangarosa EJ, et al: Shigellosis in the United States: Ten year review of nationwide surveillance, 1964-1973. Am J Epidemiol 104:543-551, May 1976

3. Nahmias AJ, Gomez-Barreto J, Kohl S, et al: Newer microbial agents in diarrhea. Hosp Pract 11:75-82, Mar 1976

4. Rosenberg ML, Hazlot KK, Schaefer J, et al: Shigellosis from swimming. JAMA 236:1849-1852, Oct 1976

5. Black RE, Craun GF, Blake PA: Epidemiology of common source outbreaks of shigellosis in the United States, 1961-1975. Am J Epidemiol 108:47-52, Jan 1978

6. Harris JC, DuPont HL, Lewis KR: Fecal leukocytes in diarrheal illness. Ann Intern Med 76:697-703, May 1972

7. Weissman JB: Infectious diarrhea: When should you start to worry. Med Times 105:63-70, Sep 1977

8. DuPont HL, Hornick RB: Adverse effect of Lomotil therapy in shigellosis. JAMA 226:1525-1528, Dec 1973

9. Haltalin KC, Kusmiesz HT, Hinton LV, et al: Treatment of acute diarrhea in outpatients. Am J Dis Child 124:554-561, Oct 1972

10. Aserkoff B, Bennett JV: Effect of antibiotic therapy in acute salmonellosis on the fecal excretion of salmonellae. N Engl J Med 281:636-640, Sep 1969

11. Rudoy RC: In vitro susceptibility of shigella strains to trimethoprim and sulfamethoxazole. Antimicrob Agents Chemother 5:439-443, May 1974

12. Gangarosa EJ: Recent developments in diarrheal diseases. Postgrad Med 62:113-117, Aug 1977

13. Satterwhite TK, DuPont HL: The patient with acute diarrhea—An algorithm for diagnosis. JAMA 236:2662-2664, Dec 1976

14. Barrett-Connor E: Shigellosis in the adult. JAMA 198:141-144, Nov 1966

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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

RESTORATION OF MOTOR FUNCTION IN THE STROKE PATIENT—A Physiotherapist's Approach—Margaret Johnstone, MCSP; Illustrated by Estrid Barton; Foreword by Professor Bernard Isaacs, MD, FRCP, Charles Hayward Professor of Geriatric Medicine, University of Birmingham. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th Street, New York City (10036), 1978. 186 pages, $8.95.

A book designed for physicial therapists and well directed to them. It does not differ remarkably from Bobath principles in the use of stimulation of reflexes to accelerate recovery from stroke. The author makes extensive use of inflatable pressure splints and of positioning.

It is a personal recounting of methods that have worked for the author, time consuming through they may be; an easily read book not directed toward physicians.

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SLEEP APNEA SYNDROMES—Kroc Foundation Series Volume 11—Editors: Christian Guilleminault, MD, Maitre de Recherche, Institut National de la Santé et Recherche Méd.cale, Paris, and Sleep Disorders Clinic and Research Center, Stanford University School of Medicine, Stanford, CA; and William C. Dement, MD, PhD, Professor of Psychiatry, Sleep Disorders Clinic and Research Center, Stanford University School of Medicine. Alan R. Liss, Inc., 150 Fifth Ave., New York City (10011), 1978. 390 pages, $34.00 (available in Europe, the UK and the Middle East exclusively from European Book Service, Hogeweyselaan 119, WEESP, The Netherlands, for 102.00 Dutch Guilders.

This book reports the proceedings of a conference held in July 1977 on a topic of considerable clinical and research interest. The emphasis is on the mechanisms and the changes involved in the two main types of sleep apnea syndromes—obstructive, or upper airway, and central sleep apneas. Most of the studies use patients, some use laboratory animals. The prevalence is not well established but felt to be related to the overall prevalence of the symptoms of daytime sleepiness and notable snoring, which are prominent in the more common obstructive type.

Although lucidly written the experimental chapters are too technical for a general audience. There is, however, something for everyone. For clinicians there are excellent overview chapters. The physiology section covers respiration, the central nervous system and the heart in sleep apnea and includes studies on blood gases, electroencephalographic changes and cardiac arrythmias. Detailed studies of the mechanisms of the obstruction include the important action of the tongue muscles among others. Although the emphasis is on the pure sleep apnea patient, some of the specific syndromes causing obstruction or a damaged respiratory center are described. These include bird-like face syndrome, poliomyelitis, Shy-Drager syndrome, myotonic dystrophy, and neurologic and neurosurgical lesions. Tracheostomy, which is in many cases curative and on occasion lifesaving for the obstructive type, is discussed in detail as is diaphragmatic pacing, the treatment for the central type.

For general readers a major review article would be more constructive. It would summarize the experimental and clinical data, some of which are necessarily repetitive. The book may serve as a reference for researchers and as a technical resource for clinicians. It provides insight for general readers into the present state of sleep research.

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THE ADOPTION TRIANGLE—The Effects of the Sealed Record on Adoptees, Birth Parents, and Adoptive Parents—Arthur D. Sorosky, MD; Annette Baran, MSW, and Reuben Pannor, MSW. Anchor Press/Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1978. 256 pages, $8.95.

It is the thesis of this text that the adoptee who is ignorant of his or her true background will be handicapped in attempting to establish psychological identity. Identity is used in concert with Erickson's developmental model. The authors believe that the adoptee will profit if the birth and other records which are usually kept secret are made available to him or her.

The basis for the text is a research report on 41 female and 9 male adoptees who responded to a request for personal experiences and reactions to standard adoptive practices. Through advertisements in newspapers and magazines these 50 adoptees and their biological parents expressed interest in telling their reactions to the traditional adoptive procedures with the secrecy that usually follows.

The authors cogently present a need to change the present adoptive practices to allow biological parents to be recontacted by adoptees if the adoptees so desire. This is not seen as a threat to the parents who adopted the child. The authors believe, based upon testimony, that adoptees would not wish to reestablish a parent-child relationship any more than would their biological parents. Such information about the biological parents would be of help in self-identification for the adoptee and helpful to the biological parent in bringing about some sense of completeness. Many of the biological parents expressed continued anxiety and concern over the adoption, even though they had made good subsequent personal adjustment with families of their own.

Since many states are moving toward even increased secrecy, this text will be fuel for a presently raging conflict in domestic courts. The small sample and the fact that volunteers responding to mass media advertisement were the bases for the text is a limiting but not a negating factor for those who would support or argue with the authors' thesis. This text is appropriate for therapists, educators and counselors who work with adoptees.

JAMES W. CROAKE, PhD
Department of Psychiatry and Behavioral Sciences
University of Washington
Seattle

in memoriam

Ahrens, Carlyle L., Long Beach. Died December 2, 1978 of heart disease, aged 85. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1923. Licensed in California in 1923. Dr. Ahrens was a member of the Los Angeles County Medical Association.

Bagatelos, Anthony P., San Francisco. Died August 21, 1979 in San Francisco of heart disease, aged 56. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1955. Licensed in California in 1955. Dr. Bagatelos was a member of the San Francisco Medical Society.

Beutel, Wolfgang W., Westlake Village. Died June 1, 1978, aged 35. Graduate of the University of Southern California School of Medicine, Los Angeles, 1971. Licensed in California in 1972. Dr. Beutel was a member of the Los Angeles County Medical Association.

Bonfilio, Victor P., San Francisco. Died July 19, 1979 in San Francisco, aged 60. Graduate of St. Louis University School of Medicine, 1947. Licensed in California in 1947. Dr. Bonfilio was a member of the San Francisco Medical Society.

Cullen, Stuart C., San Francisco. Died August 11, 1979 in Belvedere of myocardial infarction, aged 70. Graduate of the University of Wisconsin Medical School, Madison, 1933. Licensed in California in 1958. Dr. Cullen was a retired member of the San Francisco Medical Society.

DePuy, James L., Watsonville. Died in June 1979, aged 58. Graduate of the University of Michigan Medical School, Ann Arbor, 1944. Licensed in California in 1949. Dr. DePuy was a member of the Santa Cruz County Medical Society.

Funnell, Arthur B., Altaville. Died June 1, 1979 of myocardial infarction, aged 72. Graduate of the College of Physicians and Surgeons, Los Angeles, 1933. Licensed in California in 1933. MD degree from California College of Medicine, 1962. Dr. Funnell was a retired member of the San Joaquin County Medical Society.

Haag, Edgar C., Sacramento. Died August 18, 1979, aged 69. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1935. Licensed in California in 1935. Dr. Haag was a retired member of the Sacramento County Medical Society.

Horton, Hammond Spalding, Montrose. Died August 2, 1979 in Montrose of myocardial infarction, aged 73. Graduate of the University of Louisville School of Medicine, 1942. Licensed in California in 1943. Dr. Horton was a member of the Los Angeles County Medical Association.

Jensen, Joseph E., sr., Laguna Hills. Died August 26, 1978 of heart disease, aged 81. Graduate of Rush Medical College, Chicago, 1926. Licensed in California in 1940. Dr. Jensen was a member of the Los Angeles County Medical Association.

Kovitz, Louis, Los Altos. Died July 22, 1979 in Palo Alto, aged 75. Graduate of Washington University School of Medicine, St. Louis, 1929. Licensed in California in 1941. Dr. Kovitz was a retired member of the Santa Clara County Medical Society.

Miller, Joseph B., Mountain View. Died July 31, 1979 in Mountain View, aged 65. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1938. Licensed in California in 1938. Dr. Miller was a member of the Santa Clara County Medical Society.

Mugler, Frederick R., Atascadero. Died June 16, 1979 in Menlo Park, aged 94. Graduate of Cooper Medical College, San Francisco, 1910. Licensed in California in 1910. Dr. Mugler was a life member of the San Luis Obispo County Medical Society.

Pike, Catherine C., San Rafael. Died August 20, 1979 in Antwerp, Belgium of injuries received in automobile accident, aged 60. Graduate of the University of California Medical School, Berkeley-San Francisco, 1943. Licensed in California in 1943. Dr. Pike was a member of the Marin Medical Society.

Roth, Merall, San Francisco. Died July 1, 1979 in Tiburon, aged 64. Graduate of Wayne University College of Medicine, Detroit, 1941. Licensed in California in 1942. Dr. Roth was a member of the Marin Medical Society.

Shevick, Murray Paul, Riverside. Died July 28, 1979 in Riverside, aged 48. Graduate of the University of California Medical School, Berkeley-San Francisco, 1956. Licensed in California in 1957. Dr. Shevick was a member of the Riverside County Medical Association.

Sudlow, Edward L., Granada Hills. Died October 7, 1978 of arteriosclerosis, aged 80. Graduate of Western Reserve University School of Medicine, Cleveland, 1925. Licensed in California in 1930. Dr. Sudlow was a member of the Los Angeles County Medical Association.

Wilhelm, Paul L., Oakland. Died September 2, 1979 in Oakland, aged 56. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1954. Licensed in California in 1955. Dr. Wilhelm was a member of the Alameda-Contra Costa Medical Association.

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Equanil Tablets*	400 mg.	8.15		
Purepac Meprobamate	400 mg.	1.85	**6.30**	77.3%
Librium Capsules*	10 mg.	8.76		
Purepac Chlordiazepoxide HCl.	10 mg.	3.90	**4.86**	55.4%

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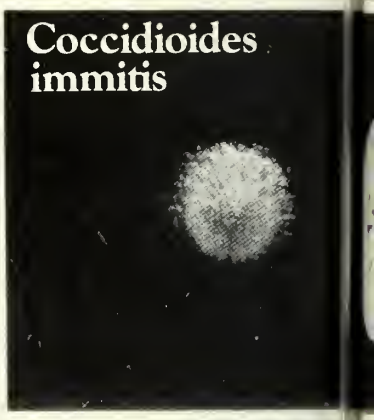
Efficacy of MONISTAT i.v. therapy...

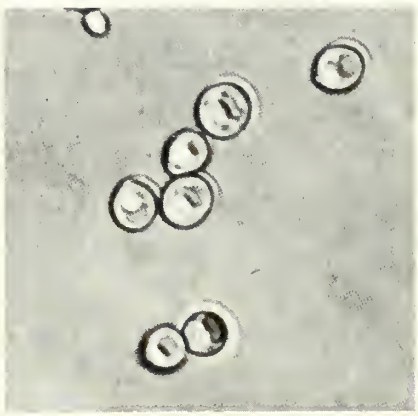
highly favorable rates of recovery or clinical improvement

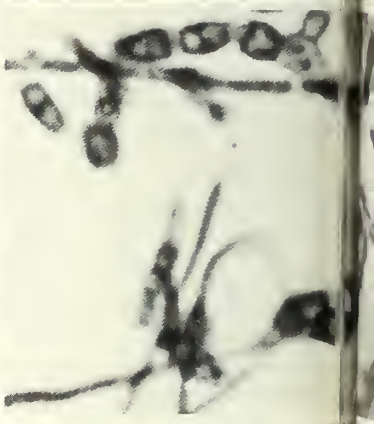
- effective against systemic candidiasis
  chronic mucocutaneous candidiasis
  coccidioidomycosis
  cryptococcosis
  paracoccidioidomycosis
- in patients who did not respond to amphotericin B therapy
- in immunologically-compromised patients with severe infections

rapid onset of clinical improvement
In most patients who responded, improvement was observed within 1-3 weeks of MONISTAT i.v. therapy; however, prolonged treatment courses may be necessary to prevent relapse.

no development of fungal resistance during therapy reported
In vitro resistance of clinical isolates has not been observed during clinical trials.







Photos courtesy of Dubos, J. R., Bacterial and Mycotic Infections of Man, J. B. Lippincott Company, 1968 and Burrows, W., Textbook of Microbiology, W. B. Saunders Company, 19th edition.

and the side effect profile

no nephrotoxicity or other permanent adverse effects in clinical studies

- even in prolonged therapy
- even in patients with renal disease

extensively evaluated
During clinical trials in over 400 patients, no permanent adverse reactions were reported.

Adverse reactions
MONISTAT i.v. should not be administered undiluted. Rapid injection of the undiluted solution may produce transient tachycardia or arrhythmia.

Adverse reactions include phlebitis, pruritus, rash, nausea, vomiting, febrile reactions, drowsiness, diarrhea, anorexia and flushes. Transient hematologic changes have occurred; therefore, the patient should be closely monitored.

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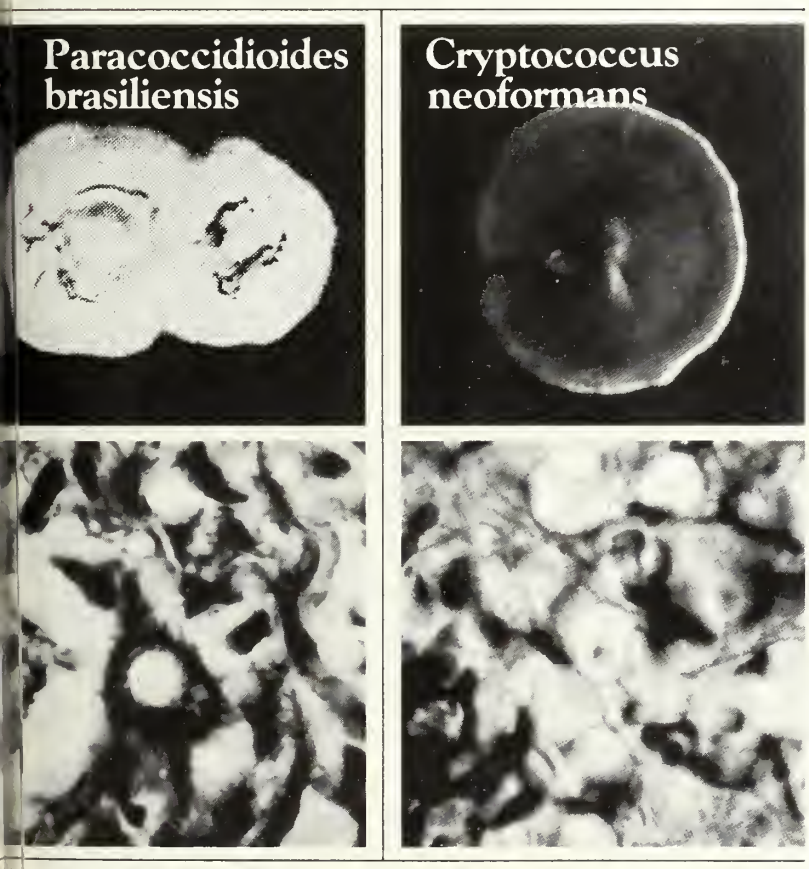
advancement systemic mycoses



generally well tolerated by severely debilitated patients

- cancer patients
- patients receiving immunosuppressive drugs
- patients with serious underlying conditions such as renal insufficiency or diabetes mellitus

for more information

Because of the uniqueness of MONISTAT i.v. only some of the highlights can be presented in this advertisement. For more information, i.e., product monograph, dosage schedules, etc., please fill out the coupon on the next page and mail to Ortho Pharmaceutical Corporation.

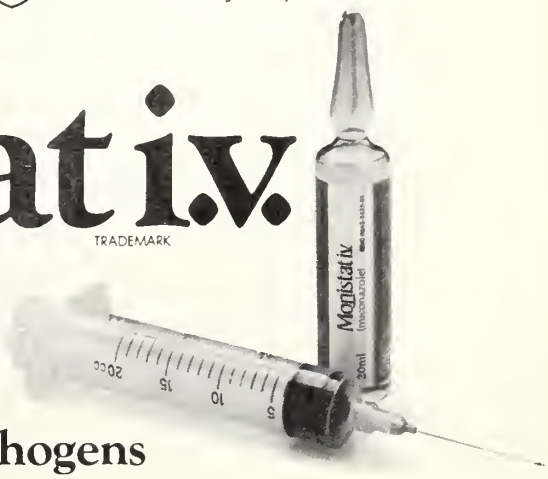
Please turn page for Prescribing Information

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

Monistat i.v.

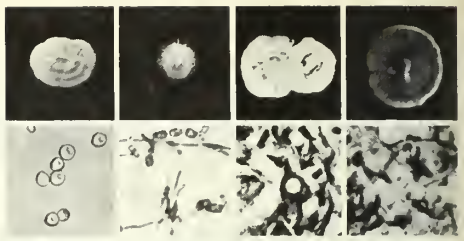
TRADEMARK

(miconazole)



broad-spectrum activity against major systemic fungal pathogens

in systemic fungal infections...



Monistat i.v.
TRADEMARK

(miconazole)

a broad-spectrum systemic antifungal agent

DESCRIPTION: MONISTAT i.v. (miconazole) 1-{2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl) methoxyl ethyl} 1 H-imidazole is a synthetic antifungal supplied as a sterile solution for intravenous infusion. Each ml of this solution contains 10 mg of miconazole with 0.115 ml PEG 40 castor oil, 1.0 mg lactic acid USP, 0.5 mg methylparaben USP, 0.05 mg propylparaben USP in water for injection. Miconazole i.v. is a clear, colorless to slightly yellow solution having a pH of 3.7 to 5.7.

CLINICAL PHARMACOLOGY: MONISTAT i.v. is rapidly metabolized in the liver and about 14% to 22% of the administered dose is excreted in the urine, mainly as inactive metabolites. The pharmacokinetic profile fits a three-compartment open model with the following biologic half-life: 0.4, 2.1, and 24.1 hours for each phase respectively. The pharmacokinetic profile of MONISTAT i.v. is unaltered in patients with renal insufficiency, including those patients on hemodialysis. The in/vitro antifungal activity of MONISTAT i.v. is very broad. Clinical efficacy has been demonstrated in patients with the following species of fungi: *Coccidioides immitis*, *Candida albicans*, *Cryptococcus neoformans*, and *Paracoccidioides brasiliensis*.

Recommended doses of MONISTAT i.v. produce serum concentrations of drug which exceed the in-vitro MIC values for the fungal species noted above. Doses above 9 mg/kg of MONISTAT i.v. produce peak blood levels above 1 μg/ml in most cases. The drug penetrates into joints.

INDICATIONS: MONISTAT i.v. is indicated for the treatment of the following severe systemic fungal infections: coccidioidomycosis, candidiasis, cryptococcosis, paracoccidioidomycosis, and for the treatment of chronic mucocutaneous candidiasis. However, in the treatment of fungal meningitis and urinary bladder infections an intravenous infusion alone is inadequate. It must be supplemented with intrathecal administration and bladder irrigation. Appropriate diagnostic procedures should be followed and MICs should be determined.

MONISTAT i.v. should not be used to treat common trivial forms of fungal diseases.

CONTRAINDICATIONS: MONISTAT i.v. is contraindicated in those patients who have shown hypersensitivity to it.

WARNINGS: Rapid injection of undiluted MONISTAT i.v., may produce transient tachycardia or arrhythmia.

PRECAUTIONS: Before a treatment course of MONISTAT i.v. is started, the physician should make sure that the patient is not hypersensitive to the drug product. MONISTAT i.v. should be given by intravenous infusion. The treatment should be started under stringent conditions of hospitalization but subsequently may be given to suitable patients under ambulatory conditions with close clinical monitoring. It is recommended that an initial dose of 200 mg be given with the physician in attendance. It is also recommended that clinical laboratory monitoring including hemoglobin, hematocrit, electrolytes and lipids be performed.

It should be borne in mind that systemic fungal mycoses may be complications of chronic underlying conditions which in themselves may require appropriate measures.

Pregnancy: Reproductive studies with MONISTAT i.v. in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus. There are no data, however, on the use of the drug in pregnant women.

Children. Since the safety of miconazole i.v. in children under one year of age has not been extensively studied, its benefits in this age group must be weighed against the possible risks involved.

ADVERSE REACTIONS: Adverse reactions which have been observed with MONISTAT i.v. therapy include phlebitis, pruritus, rash, nausea, vomiting, febrile reactions, drowsiness, diarrhea, anorexia and flushes. In the U.S. studies, 29% of 209 patients studied had phlebitis, 21% pruritus, 18% nausea, 10% fever and chills, 9% rash, and 7% emesis. Transient decreases in hematocrit and serum sodium values have been observed following infusion of MONISTAT i.v. Thrombocytopenia has also been reported. No serious renal or hepatic toxicity has been reported. If pruritus and skin rashes are severe, discontinuation of treatment may be necessary. Nausea and vomiting can be mitigated with antihistaminic or antiemetic drugs given prior to MONISTAT i.v. infusion, or by reducing the dose, slowing the rate of infusion, or avoiding administration at mealtime.

Aggregation of erythrocytes or rouleau formation on blood smears has been reported. Hyperlipemia has occurred in patients and is reported to be due to the vehicle. Cremophor EL (PEG 40 castor oil).

DRUG INTERACTIONS: Drugs containing cremophor-type vehicles are known to cause electrophoretic abnormalities of the lipoprotein. These effects are reversible upon discontinuation of treatment but are usually not an indication that treatment should be discontinued.

Interaction with the coumarin drugs resulting in an enhancement of the anticoagulant effect has also been reported. In cases of simultaneous treatment with MONISTAT i.v. and coumarin drugs, the anticoagulant effect should be carefully titrated since reductions of the anticoagulant doses may be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE

Adults. The doses may vary with the diagnosis and with the infective agent, from 200 to 1200 mg per infusion. The following daily doses, which may be divided over 3 infusions, are recommended:

Organism	Dosage Range*	Duration of Successful Therapy (weeks)
Coccidioidomycosis:	1800 to 3600 mg per day	3 to > 20
Cryptococcosis:	1200 to 2400 mg per day	3 to > 12
Candidiasis:	600 to 1800 mg per day	1 to > 20
Paracoccidioidomycosis:	200 to 1200 mg per day	2 to > 16

* May be divided over 3 infusions.

Repeated courses may be necessitated by relapse or reinfection.

Children: A total daily dose of about 20 to 40 mg/kg is generally adequate. However, a dose of 15 mg/kg body weight per infusion should not be exceeded.

ADMINISTRATION: MONISTAT i.v. should be diluted in at least 200 ml of fluid. The diluent of choice is 0.9% sodium chloride or alternatively Dextrose 5% injectable solution. The intravenous infusion should be given over a period of 30 to 60 minutes.

Generally, treatment should be continued until all clinical and laboratory tests no longer indicate that active fungal infection is present. Inadequate periods of treatment may yield poor response and lead to early recurrence of clinical symptoms. The dosing intervals and sites and the duration of treatment vary from patient to patient and depend on the causative organism.

OTHER MODES OF ADMINISTRATION: Intrathecal. Administration of the undiluted injectable solution of MONISTAT i.v. by the various intrathecal routes (20 mg per dose) is indicated as an adjunct to intravenous treatment in fungal meningitis. Succeeding intrathecal injections may be alternated between lumbar, cervical, and cisternal punctures every 3 to 7 days. Bladder instillation of 200 mg of diluted solution is indicated in the treatment of mycoses of the urinary bladder.

HOW SUPPLIED: MONISTAT i.v. is supplied in 20 ml ampoules.

MONISTAT i.v. (miconazole) is an original product of Janssen Pharmaceutica N.V., Belgium, and co-developed by Ortho Pharmaceutical Corporation.

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

WJ10/79

Ortho Pharmaceutical Corporation
c/o 733 Summer Street
Stamford, CT 06901

Please send me more information on the broad-spectrum, systemic antifungal agent... MONISTAT i.v. (miconazole).

_____ M.D.

Address _____

City _____ State _____ Zip _____

Specialty _____

October 1978

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

HEMATOLOGIC PROBLEMS IN RENAL DISEASE—Edited by Joanne H. Jepson, MD, Chief, Division of Hematology and Oncology, The Medical College of Pennsylvania and Hospital, Philadelphia. Addison-Wesley Publishing Co., Medical/Nursing Division, 2727 Sand Hill Road, Menlo Park, CA (94025), 1979. 350 pages, $38.50.

THE HERITAGE OF AVIATION MEDICINE—An Annotated Directory of Early Artifacts—Compiled by Robert J. Benford, MD, Colonel, U.S. Air Force (Ret). Aerospace Medical Association, Washington National Airport, Washington, DC (20001), 1979. 132 pages, $4.50 postpaid (soft cover).

HUMANISM AND THE PHYSICIAN—Edmund D. Pellegrino, MD, president of The Catholic University of America and professor at Georgetown University; founding editor of the **Journal of Medicine** and director of the Institute on Human Values in Medicine. The University of Tennessee Press, Knoxville (37916), 1979. 248 pages, $15.50.

LOW FRICTION ARTHROPLASTY OF THE HIP—Theory and Practice—Professor Sir John Charnley, CBE, FRS, FRCS, FACS, Emeritus Professor of Orthopaedic Surgery, University of Manchester, Honorary Orthopaedic Surgeon, Centre for Hip Surgery, Wrightington Hospital, Consultant Orthopaedic Surgeon, King Edward VII Hospital, Midhurst, Sussex. Springer-Verlag New York Inc., 44 Hartz Way, Secaucus, NJ (07094), 1979. 376 pages, with 440 figures, 205 in color, $48.00.

MECHANISMS OF INTESTINAL SECRETION—Volume 12 in the Kroc Foundation Series—Editor: Henry J. Binder, MD, Professor of Medicine, Yale University School of Medicine. Alan R. Liss, Inc., 150 Fifth Avenue, New York City (10011), 1979. 319 pages, $28.00; available in Europe, the UK and the Middle East exclusively from: European Book Service, Flevolaan 36-38, P.O.B. 124, 1380 AC Weesp, Holland; price: Dfl. 84.00.

NEONATAL PULMONARY CARE—Edited by Donald W. Thibeault, MD, The Children's Mercy Hospital, University of Missouri, Kansas City, School of Medicine; and George A. Gregory, MD, Professor of Anesthesia and Pediatrics, Cardiovascular Research Institute, University of California, San Francisco. Addison-Wesley Publishing Company, Inc., Health Sciences Div., 2727 Sand Hill Road, Menlo Park, CA (94025), 1979. 480 pages, $34.50.

ORTHOPAEDICS IN PRIMARY CARE—Chinni Pennathur Ramamurti, MD, FRCS, FAAOS, Chief of Orthopaedics, Group Health Cooperative of Puget Sound, Clinical Associate Professor of Orthopaedics, University of Washington School of Medicine; edited by Richard Vernon Tinker, MD, Associate Director, Family Practice Residency Program, Group Health Cooperative of Puget Sound. The Williams & Wilkins Company, 428 E. Preston Street, Baltimore (21202), 1979. 385 pages, $36.00.

PRIMARY CARE OF HAND INJURIES—William L. Newmeyer, MD, Assistant Clinical Professor of Surgery, University of California, San Francisco. Lea & Febiger, 600 Washington Square, Philadelphia (19106), 1979. 297 pages, $22.50.

RECENT ADVANCES IN HISTOPATHOLOGY—Number Ten—Edited by P. P. Anthony, MB, BS, MRCPATH, Consultant Pathologist and Senior Lecturer in Pathology, Devon Area Health Authority and University of Exeter; formerly Senior Lecturer in Pathology, The Middlesex Hospital Medical School, University of London; and N. Woolf, PhD, MMED(PATH), FRCPATH, Bland-Sutton Professor of Histopathology, The Middlesex Hospital Medical School, University of London. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 356 pages, $27.50.

REVERSIBILITY OF FEMALE STERILIZATION—Edited by I. Brosens, Department of Gynaecology, Academisch Ziekenhuis Sint-Rafael, Leuven, Belgium; and R. Winston, Department of Gynaecology, Hammersmith Hospital, London. U.K. edition published and distributed by Academic Press Inc., London; U.S. edition published and distributed by Grune & Stratton Inc., 111 Fifth Avenue, New York City (10003), 1978. 194 pages, $15.50.

REVIEW OF ALLIED HEALTH EDUCATION: 3—General Editor: Joseph Hamburg, Dean, College of Allied Health Professions, University of Kentucky; Associate Editors: Darrel J. Mase, Dean and Professor Emeritus, University of Florida College of Health Related Professions and J. Warren Perry, Dean, School of Health Related Professions, State University of New York at Buffalo. The University Press of Kentucky, Lexington (40506), 1979. 156 pages, $7.50.

(Continued on Page 25)

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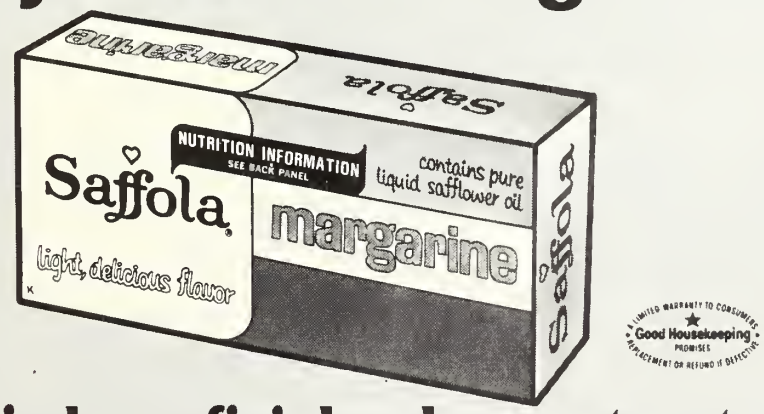

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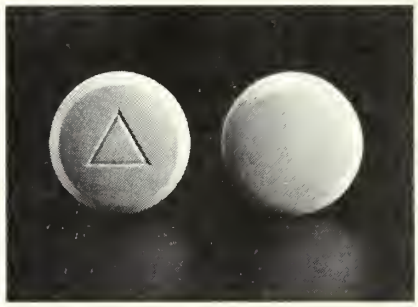
Saffola is beneficial as part of a fat modified diet to help reduce serum cholesterol.

The Maker

Examining a Few Myths About Prescribing.



Increasing pressure is being put on the practicing physician to prescribe drugs generically. You are told that brand-name products are universally "expensive" and generic versions are relatively "cheap." To make this case, the most extreme (rather than typical) price differentials are cited. Thus, consumers are led to believe that such differentials are commonplace. Even your knowledge and your motives as a physician are questioned.

Understandably, these views have created myths. We think it's time to examine them in the light of all the facts and ramifications.

MYTH: There are no differences in quality and performance between brand-name products and their generic counterparts. The corollary is that there are no differences among products made by high-technology, quality-conscious, research-based companies and those made by commodity-type suppliers.

FACT: The Food and Drug Administration does a good job in monitoring a generally excellent drug supply. Still, it has nowhere near the resources to guarantee the quality and bioavailability of all marketed products at any given time. Just a few months ago, for example, it noted that batches of tetracycline HCl capsules which met official monograph requirements were not bioequivalent to a reference product. As you know, there is substantial literature on this subject affecting many drugs, including such antibiotics as tetracycline and erythromycin. The record on drug recalls and court actions affirms strongly that there are differences among pharmaceutical companies and their products. Research-intensive companies have far better records than those that do no research and may practice minimum quality assurance.

MYTH: Industry favors only "expensive" brand names and denigrates all generics.

FACT: PMA companies make 90 to 95 percent of the drug supply, including, therefore, most of the generics. Drug nomenclature is not the important point; it's the competence of the manufacturer and the integrity of the product that count.

Matters.

MYTH: Generic options almost always exist.

FACT: About 55 percent of prescription drug expenditure is for single-source drugs. This means, of course, that for only 45 percent of such expenditure, is a generic prescribing option available.

MYTH: Generic prescriptions are filled with inexpensive generics, thus saving consumers large sums of money.

FACT: Market data show that you invariably prescribe—and pharmacists dispense—both brand and generically labeled products from known and trusted sources, in the best interest of patients. In most cases the patient receives a proven brand product. Savings from voluntary or mandated generic prescribing are grossly exaggerated.

MYTH: Drugs account for a major portion of the rise in health care costs.

FACT: Drugs represent a very small part of such costs. The amount of the health care dollar spent for prescription drugs was about 12 cents in 1967; today it is about 8 cents. And you as a physician are most conscious of how drug therapy can cut hospitalization, avert surgery, reduce office visits and keep patients on the job.

MYTH: Government intrusions into the marketplace will save tax money.

FACT: Government schemes always cost the taxpayer something, and the costs often exceed the benefits. Certainly, any federal "help," such as lists of wholesale drug prices sent to all physicians and pharmacists, will be no exception. Just think of the expense of keeping them current! Moreover, wholesale prices are poor guides to actual transaction prices and even worse guides to retail prices.

The PMA Position

We believe your freedom to prescribe, either by generic or brand name, should be totally unabridged. Otherwise, your prescribing prerogatives and your relationships with patients will be seriously impaired.

The maker does matter

After the myths about price and equivalency have been shattered, one fact stands out more clearly than ever: *The maker does matter.* As always, your best guide to drug therapy for your patients is to select products—both brands and generics—from manufacturers with credentials and performance records you have come to respect.

PMA

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005

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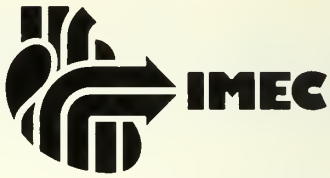

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REVIEW OF MEDICAL PHYSIOLOGY — Ninth Edition — William F. Ganong, MD, Professor and Chairman, Department of Physiology, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1979. 618 pages, $14.00.

ROCKEFELLER MEDICINE MEN—Medicine and Capitalism in America—E. Richard Brown, University of California, Los Angeles, School of Public Health. University of California Press, 2223 Fulton St., Berkeley, CA (94720), 1979. 293 pages, $12.95.

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THE SIDE EFFECTS OF ESTROGEN DRUG THERAPY: Contraception and Postmenopause—Harold E. Simmons. Psychogenic Disease Publishing Company, P.O. Box 19098, Sacramento, CA (95819), 1979. 92 pages, $4.95 (softbound).

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REFERENCES

1. Baiocchi O: Jornal Brasileiro de Ginecologia, September, 1973
2. Leibsohn E, Bagatell FK: Brit J Derm 90:435-440, 1974
3. Reinhard W, Weber G, Petres J: Zeitschrift für Hautkrankheiten, April, 1974
4. Jonquieres EDL, Favere M, Pasut H: La Semana Médica 144:447-449, 1974
5. Cordero A: La Semana Médica 145:145-148, 1974
6. Bagatell FK: Cutis 14:459-462, 1974
7. Lepaw MI: Scientific Exhibit presented at Dec., 1974, meeting of American Academy of Dermatology, Chicago, IL
8. Theodorides A, Stratigos I, Vareltsides A, et al: Iatrikā Chronikā 14:559-574, 1974
9. Clark RF, Clement ER: Arch Derm 111:731-733, 1975
10. Sudilovsky A, Clewe TH: Clin Pharmacol 15:779-784, 1975
11. Turnbull BC: Aust J Derm 16:17-19, 1975
12. Bleeker J: Curr Med Res Opinion 3:225-228, 1975
13. Savin RC: J Int Med Res 4:34-36, 1976
14. Kanof NB, Blau S: Cutis 17:796-798, 1976
15. Close JE: Int J Derm 15:534-537, 1976
16. Lepaw MI: Cutis 21:571-573, 1978
17. Savin RC: Dermatology 1:34-38, 1978
18-21. Data on file at Squibb Institute for Medical Research

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(Continued from Page 30)

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SITUATIONS WANTED

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FAMILY PHYSICIAN seeks family practice group affiliation in S.F. Bay Area in **mid 1980.** 36 years old, residency trained and AAFP board certified. Four years private family practice and 3 years emergency room practice. Write Box 6064, The Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

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(Continued on Page 34)

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(Continued from Page 32)

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SPEAKERS

Diagnostic Radiology

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Phillip H. Cook, Professor and Chairman Department of Radiology, Peter Brent Brigham Hospital, Boston

MORTON A. BOSNIAK, MD
New York Univ. Medical Center, New York

FRIEDA FELDMAN, MD
Columbia Presbyterian Med. Center, New York

ANDREW K. POZNANSKI, MD
Children's Memorial Hospital, Chicago

STUART S. SAGEL, MD
Mallinckrodt Institute, St. Louis

JOSEPH P. WHALEN, MD
New York Hospital-Cornell Med. Ctr., New York

Nuclear Medicine

BARRY A. SIEGEL, MD
Mallinckrodt Institute, St. Louis

Ultrasound

MICHAEL L. JOHNSON, MD
Univ. of Colorado Med. Center, Denver

Radiation Therapy-Oncology

RAYMOND S. BUSH, MD, FRCP(C)
Ontario Cancer Institute, Toronto

GEORGE CANELLOS, MD
Sidney Farber Cancer Institute, Boston

JAMES D. COX, MD
Medical College of Wisconsin, Milwaukee

B. J. KENNEDY, MD
Univ. of Minn.-Masonic Mem. Hosp., Minneapolis

CLIFTON F. MOUNTAIN, MD
M. D. Anderson Tumor Institute, Houston

MICHAEL JOHN PECKHAM, MD, MRCP, FRCR
Royal Marsden Hospital, London, England

Workshop Instructors

MARC N. COEL, MD
University of California, San Diego

GLORIA FRANKL, MD
Kaiser Permanente Hospital, Los Angeles

BARBARA B. GOSINK, MD
University of California, San Diego

JAMES M. HALLS, MD
L.A. County-USC Medical Center, Los Angeles

ANTON HASSO, MD
Loma Linda University Hospital, Loma Linda, CA

GEORGE R. LEOPOLD, MD
University of California, San Diego

CHARLES SCHATZ, MD
Hollywood Presbyterian Hospital, Los Angeles

TOM W. STAPLE, MD
Memorial Hospital Medical Center, Long Beach

Registration: Fee of $140 includes two luncheons, $75 for residents, $100 for L.A.R.S. members. Workshops: $30 each.
Advance Registration: Nathan Green, MD, 15107 Vanowen Street, Van Nuys, California 91405
Hotel Accommodations: Convention Manager, Century Plaza Hotel, Los Angeles, California 90067
Message Center: Century Plaza Hotel (213) 277-2000

HAWAII POST CONVENTION SEMINAR: January 27 through February 3, 1980. $762 per person includes air fare from Los Angeles, transportation and accommodations. **There will be a $250 tuition fee for each registrant. This is accredited for 20 hours of AMA Category I credit.**

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This listing of continuing education programs in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

October 20-24—**American Society of Anesthesiologists—Annual Meeting.** Hilton, San Francisco. Saturday-Wednesday. Contact: William S. Marinko, Asst. Exec. Sec., ASA, 515 Busse Highway, Park Ridge, IL 60068. (312) 825-5586.

October 25-November 2—**Post ASA Hawaiian Seminar.** Kona Village Resort, Hawaii. 9 days. 28 hrs. Contact: Adham Safwat, Box 7550, Menlo Park 94025. (415) 494-3799.

October 26-28—**Clinical Anesthesia Monitoring.** Anesthesiology Educational Foundation and Calif. Soc. of Anesthesiologists at Holiday Inn, Monterey. Friday-Sunday. Contact: AEF, P.O. Box 24230, Federal Bldg., Los Angeles 90024.

January 8-12—**Anesthesia Update.** UCSD at Hotel del Coronado. Tuesday-Saturday. 20 hrs. $200.

January 25-27—**Pediatric Anesthesiology—18th Clinical Conference.** Childrens Hospital at Marriott, Los Angeles. Friday-Sunday. 15 hrs. $160. Contact: Wayne Herbert, MD, P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

February 7-10—**7th Neonatal and Infant Respiratory Symposium.** Ohio State Univ., Dept. of Anesthesiology, at Marriott, Los Angeles. Thursday-Sunday. Contact: John S. McDonald, MD, Dept. of Anesthesiology, OSU, 410 W. 10th Ave., Columbus, OH 43210. (614) 422-5591.

March 30-April 5—**Obstetric Anesthesia.** Ohio State University, Dept. of Anesthesiology, at Sheraton Waikiki Hotel, Oahu, Hawaii. One week. Contact: John S. McDonald, MD, Dept. of Anesthesiology, OSU, 410 W. 10th Ave., Columbus, OH 43210. (614) 422-5591.

CANCER

October 27—**New Methods for Fighting Cancer.** San Francisco Regional Cancer Foundation at Letterman Army Hospital, San Francisco. Saturday. 4 hrs. Contact: Dr. Terry Sheehy, S.F. Regional Cancer Foundation, 14th and Lake, San Francisco 94118. (415) 221-2132.

October 31-November 2—**Cancer Symposium—3rd Annual.** Scripps Memorial Hospital at Holiday Inn at the Embarcadero, San Diego. Wednesday-Friday. 22 hrs. $250. Contact: Nomi Feldman, Conf. Coordinator, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

November 9-10—**Gynecologic and Breast Cancer: Current Concepts and Controversies.** Mt. Zion Hospital and Medical Center at Fairmont Hotel, San Francisco. Friday-Saturday. Contact: Office of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

November 12—**Medical Management of Hodgkin's Disease.** San Joaquin Community Hospital, Bakersfield. Monday. 1 hr. Contact: Oncology Services, San Joaquin Community Hosp., 2615 Eye St., Bakersfield 93301. (805) 327-1711, ext. 363.

December 12—**15th Annual Northern California Cancer Conference.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 7 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Memorial Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 284.

January 16—**Testicular Tumors.** Hospital of the Good Samaritan at Bonaventure, Los Angeles. Wednesday. Contact: Janie Sternal, Cont. Med. Ed., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

March 21—**Annual Cancer Symposium.** California Hospital Medical Center, Los Angeles. Friday. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411, ext. 251.

EMERGENCY MEDICINE

October 22—**Dermatology for the Emergency Room.** General Hosp. Ventura Co. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at General Hosp., Ventura. Monday; 8:00 p.m. 1½ hrs. (CMA and ACEP). Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

November 30-December 1—**Emergency Medicine.** UCLA at Miramar-Sheraton, Santa Monica. Friday-Saturday. 13½ hrs. $160.

December 6-7—**Advances in Emergency Medicine.** UCSF. Thursday-Friday.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Lolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

December 6-8—**Trauma.** See Surgery, December 6-8.

December 6-8—**Hand and Wrist Trauma.** See Surgery, December 6-8.

December 10-14—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $350.

December 14-16—**Critical Care Medicine: Taking Stock of Shock.** See Of Interest To All, December 14-16.

December 15—**Physical Assessment and Diagnosis Course for Emergency and Primary Care Physicians.** Memorial Hospital Medical Center, Long Beach. Saturday. 6 hrs. $65. Contact: Program Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

January 14-18—**Medical Management of EMS Systems.** UCSD at Hilton, San Diego, Monday-Friday. 36 hrs.

January 21-25—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

January 21-25—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

February 11-15—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

March 17-21—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

MEDICINE

October 15-19—**Advanced Course for Internists.** STAN at Hyatt on Union Square, San Francisco. Monday-Friday. 25 hrs. $290.

October 18-20—**Cardiology Update—1979.** American College of Cardiology at Del Monte Hyatt, Monterey. Saturday-Monday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

October 18-20—**Rheumatology Update—1979.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Saturday. 16 hrs. $165.

October 18-21—**Society of Nuclear Medicine—4th Annual Western Regional Meeting.** Monterey Conference Center, Monterey. Thursday-Sunday. Contact: Justine Parker, Western Regional Chapters, Society of Nuclear Medicine, P.O. Box 40279, San Francisco 94140. (415) 647-0722.

October 19-20—**Mycology Review** (a course for residents in dermatology and pathology). STAN. Friday-Saturday. 16 hrs. $50 per day; $25 per day for residents and trainees. Contact: Paul H. Jacobs, MD, Dept. of Derm., Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

October 19-20—**Vascular Disorders and the Primary Care Physician.** UCSF at Fairmont Hotel, San Francisco. Friday-Saturday. 11 hrs. $130, both days; $80, one day.

October 20-27—**British Clinical Cardiology in the Paul Wood Tradition.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $325.

October 22—**Respiratory Diseases Due to Pollutants.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

October 24—**Diabetes Mellitus Symposium.** Hospital of the Good Samaritan at Biltmore, Los Angeles. Wednesday. 7 hrs. $70. Contact: Janie Sternal, Cont. Med. Ed., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

November 1-2—**Symposium on Thyroid Disease, Parathyroid Disease, and Vitamin D Metabolism.** Providence Hospital and Endocrine-Metabolic Center at Hilton, San Francisco. Thursday-Friday. 18 hrs. $200. Contact: Endocrine-Metabolic Ctr., P.O. Box 23020, Oakland 94623. (415) 835-4940.

November 2-3—**California Society of Internal Medicine—Annual Meeting.** Hotel del Coronado, Coronado. Friday-Saturday. Contact: CSIM, 703 Market St., 1412 Central Tower, San Francisco 94103. (415) 362-1548.

November 2-4—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Jack Tar Hotel, San Francisco. Friday-Sunday. 13 hrs. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

November 3—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Sch. of Med., Stanford 94305. (415) 497-6101.

November 4-6—**Fifth Annual Workshop on the Thyroid.** American Thyroid Assn. at Golden Gateway Holiday Inn, San Francisco. Sunday-Tuesday. 14 hrs. $200. Contact: Dr. Lewis Braverman, Univ. of Mass. Med. Ctr., 55 Lake Ave., N., Worchester, MA 01605.

November 5-9—**Update on Dermatology and Rheumatology for the Practicing Physician.** Scripps Clinic and Research Foundation at Islandia Hyatt, San Diego. Monday-Friday. 35 hrs. $325. Contact: Nomi Feldman, Conf. Coordinator, Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100, ext. 8214.

November 5-14—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

November 8-10—**Coronary Artery Disease: Medical and Surgical Decisions.** Eisenhower Medical Center at Marriott Las Palmas Resort, Rancho Mirage. Thursday-Saturday. Contact: John J. Deller, MD, Dir. of Ed. and Research, Eisenhower Med. Ctr., 39000 Bob Hope Dr., Palm Desert 92260. (714) 346-3911.

November 9—**Venous Thromboembolism.** PMC and American Heart Assn. Friday. 6 hrs. $25.

November 10—**Viral Diseases in Clinical Practices.** Alta Bates Hospital, Berkeley. Saturday. 6 hrs. Contact: Claudia Read, Med. Ed., Alta Bates Hosp., 3001 Colby St., Berkeley 94705. (415) 845-7110, ext. 2055.

November 10-11—**What's New in Renal and Hypertensive Disease?** UCLA. Saturday-Sunday. 14 hrs. $160.

November 15-16—**Neurology Update.** UCSD at Vacation Village, San Diego. Thursday-Friday.

November 15-17—**Advanced Cardiopulmonary Care.** PMC at Holiday Inn-Financial District/Presbyterian Hospital, San Francisco. Thursday-Saturday. 12 hrs. lecture; 18 hrs. lecture and workshop. $150 for lecture; $235, lecture and workshop.

November 30—**The Problems of Essential Hypertension in the 1980's.** UCD at Red Lion Motor Inn, Sacramento. Friday. 7 hrs. $25.

November 30-December 1—**Practical Endocrinology for Primary Care Physicians.** UCLA. Friday-Saturday.

November 30-December 2—**Concepts of Common Infectious Diseases.** UCSD at Hilton, San Diego. Friday-Sunday. 15 hrs. $175.

December 1-2—**Practical Endocrinology for Primary Care Physicians.** UCLA. Saturday-Sunday.

December 6-7—**5th Annual Lyman A. Brewer, III, Cardiothoracic Symposium—The Esophagus.** White Memorial Medical Center at Bonaventure Hotel, Los Angeles. Thursday-Friday. Contact: Dir., Dept. of CME, White Memorial Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 263-6100 or (213) 268-5000.

December 6-9—**Neurotology Workshop.** PMC at Ilikai Hotel, Honolulu. Thursday-Sunday. 24 hrs. $435.

December 7-8—**Allergy/Immunology, Infectious Diseases, Endocrinology/Metabolism, Oncology.** American College of Physicians at San Francisco. Friday-Saturday. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200.

December 7-9—**Advances in Heart Disease 1980—12th Annual Seminar on Clinical Cardiology.** American College of Cardiology at Fairmont Hotel, San Francisco. Friday-Sunday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

December 12—**Management of Hypertension.** LLU. Wednesday. 4 hrs.

January 2—**Practical Gastroenterology for Primary Care Physicians.** UCLA. Saturday.

January 6-13—**Echocardiography in Hawaii.** Honolulu Medical Group Research and Education Foundation, Univ. of Hawaii School of Medicine, Univ. of Rochester School of Medicine at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 18 hrs. Contact: Echocardiography in Hawaii, Honolulu Med. Grp. Research and Ed. Fnd., 550 S. Beretania St., Honolulu 96813. (808) 537-2211.

January 8-12—**Intensive Review of Common Allergic and Asthmatic Diseases.** UCD at Inter-Continental Hotel, Maui, Hawaii. Tuesday-Saturday. 25 hrs. $250.

January 20-24—**Angiography and Vascular Disease.** UCSD at Vacation Village, San Diego. Sunday-Thursday. 26 hrs. $325.

January 26—**Asthma and Allergies.** UCLA. Saturday.

January 31-February 1—**Hypertension: Advances in Treatment.** American Heart Assn., Orange Co. Chap., at Registry Hotel, Irvine. Thursday-Friday. Contact: AHA, Orange Co. Chap., 1043 Civic Center Dr. West, Santa Ana 92703. (714) 547-3001.

January 31-February 2—**Fundamentals of Echocardiography—An Introductory Course for Clinicians.** American College of Cardiology at Century Plaza, Los Angeles. Thursday-Saturday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 2—**Pediatric Dermatology Seminar.** STAN. Saturday. Contact: Paul H. Jacobs, MD, Dept. of Derm., Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

February 7-9—**Tri-State Symposium on Clinical Cardiology.** American Heart Assn.'s Council on Clinical Cardiology; AHA, Greater Los Angeles, Arizona and New Mexico Affiliates, at Disneyland Hotel, Anaheim. Thursday-Saturday. 15 hrs. $200, Heart Assn. member; $250, nonmember. Contact: LaVerna Titus, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

February 13—**Chronic Obstructive Pulmonary Disease.** LLU. Wednesday. 4 hrs.

February 13-15—**Advances in Neurology.** UCSF. Wednesday-Friday.

February 13-15—**Cardiovascular Disease—1980: Advances in Diagnosis and Management.** American College of Cardiology at Vacation Village, San Diego. Wednesday-Friday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 16—**5th Annual Liver Conference, Cholestasis.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 7 hrs. $105. Contact: Prog. Coord., Ctr. for Health Ed., 2801 Atlantic Ave, Long Beach 90801. (213) 595-3811.

February 21-24—**Federation of Western Societies of Neurological Science—Annual Meeting.** Biltmore Hotel, Santa Barbara. Thursday-Sunday. Contact: J. Carroll Ramseyer, MD, EEG/EMG Laboratory, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017.

February 22-23—**Medical Knowledge Self Assessment II.** American College of Physicians and PMC at Hyatt Regency, San Francisco. Friday-Saturday. 12 hrs. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

March 7-9—**Northern California-Nevada Regional Meeting, American College of Physicians.** Doubletree Inn, Monterey. Friday-Sunday. Contact: Ralph O. Wallerstein, MD, 3838 California St., San Francisco 94118.

March 16-19—**Basic Cardiology for the Primary Care Physician.** UCSF at Yosemite. Sunday-Wednesday.

March 24-26—**4th Annual Review and Update of the Immunology and Clinical Practice of Allergy.** USCD at Hilton, San Diego. Monday-Wednesday. 20 hrs. $210.

OBSTETRICS AND GYNECOLOGY

October 17-21—**Pacific Coast Fertility Society—27th Annual Meeting.** Marriott's Rancho Las Palmas, Rancho Mirage. Wednesday-Sunday. Contact: PCFS, 5820 Wilshire Blvd., Suite 500, Los Angeles 90036. (213) 937-5514.

November 5-8—**Advancing Perinatology into the 1980's.** UCSD at Vacation Village, San Diego. Monday-Thursday.

November 9-11—**Peripartum Period.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Friday-Sunday. 6 hrs. $150. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 29-December 1—**Controversies in Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Canyon Hotel, Palm Springs. Thursday-Saturday. 18 hrs. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 6-9—**Gynecologic Urology: Theory and Practice, Basic and Advanced.** Memorial Hospital Medical Center-UCI Center for Health Education at Sheraton-Universal, Hollywood. Thursday-Sunday. 20 hrs. $325. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 7-8—**Adolescent Sexuality and Gynecology.** PMC. Friday-Saturday. 9 hrs. $125.

January 23-26—**Clinical Obstetrics and Gynecology and Histological Pathology.** UCI and Women's Hospital of Long Beach at Newporter Inn, Newport Beach. Wednesday-Saturday. 26 hrs. $250. Contact: Prog. Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801.

February 9-10—**Obstetrical and Gynecological Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton, Beverly Hills. Saturday-Sunday. 10 hrs. $70. Contact: Miss Dee Davis, Exec. Sec., 5820 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

March 12—**Vaginitis.** LLU. Wednesday. 4 hrs.

PEDIATRICS

November 3, February 2, May 3—**Developmental Disabilities: Recent Developments and Trends.** See Psychiatry, November 3, February 2, May 3.

November 12-14—**Primary Care Pediatrics.** UCI at Marriott Inn, Newport Beach. Monday-Wednesday. 17 hrs.

November 16—**Phil Rothman Memorial Lecture.** Childrens Hospital of Los Angeles. Friday. Contact: Robert Romans, MD, Cont. Med. Ed., Childrens Hosp., P.O. Box 54700, Terminal Annex, Los Angeles 90054. (213) 669-2518.

November 16-19—**Las Vegas Seminars.** American Academy of Pediatrics, Calif. Chapters 1, 2, 3, at Hilton Hotel, Las Vegas. Friday-Monday. $175, members; $200, nonmembers. Contact: AAP, Chap. 2, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

November 26-29—**Developmentally Disabled Child.** UCSD at Vacation Village, San Diego. Monday-Thursday.

December 6-8—**Pediatric Allergy/Immunology.** UCSF. Thursday-Saturday.

February 2—**Pediatric Dermatology Seminar.** See Medicine, February 2.

February 4-6—**Pediatric Nephrology and Urology.** UCSD at Vacation Village, San Diego. Monday-Wednesday.

February 23—**Pediatric Review.** UCLA. Saturday.

March 8—**Adolescent Medicine.** UCLA. Saturday.

PSYCHIATRY

October 20—**The Borderline Personality—Diagnosis and Treatment.** Northern Calif. Psychiatric Society and McAuley Institute at St. Mary's Hospital, San Francisco. Saturday. 3 hrs. $15. Contact: NCPS, 1631 Ocean Ave., San Francisco 94112.

October 26—**Interviewing Skills in Psychiatry.** PMC at Los Angeles. Friday. 4 hrs. $25.

October 27—**Psychiatry Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 7 hrs. Contact: Prog. Coordinator, UCI Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 28-31—**Academy of Psychosomatic Medicine—Annual Meeting.** Fairmont Hotel, San Francisco. Sunday-Wednesday. Contact: Thomas C. Nelson, Exec. Dir., 70 W. Hubbard, Suite 202, Chicago, IL 60610. (312) 644-2623.

October 28-31—**Therapeutic Guided Imagery.** UCLA at Yosemite. Sunday-Wednesday.

November 3—**Current Concepts in Sleep Disorders.** Northern Calif. Psychiatric Society and McAuley Institute at St. Mary's Hospital, San Francisco. Saturday. 3 hrs. $15. Contact: NCPS, 1631 Ocean Ave., San Francisco 94112.

November 3—**Interviewing Skills in Psychiatry.** PMC. Saturday. 4 hrs. $25.

November 3, February 2, May 3—**Developmental Disabilities: Recent Developments and Trends.** UCLA. 3 Saturdays.

November 9-11—**World of Family Therapy Symposium.** UCSF. Friday-Sunday. 10 hrs. $55.

November 16—**Interviewing Skills in Psychiatry.** PMC at San Diego. Friday. 4 hrs. $25.

November 26-30—**Group Therapy Seminars.** UCSF at VA Hospital, Oakland. Monday-Friday. 31 hrs. $50.

December 3-14—**Mental Retardation, Psychiatry and Primary Care.** UCLA. 2 weeks.

December 14—**Interviewing Skills in Psychiatry.** PMC at Anaheim. Friday. 4 hrs. $25.

January 18-20—**Brief Psychotherapy.** UCSF. Friday-Sunday.

January 27-February 1—**Midwinter Program in Continuing Education for Psychiatrists—6th Annual.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday. 26 hrs. $200.

February 2—**Dealing with Depression.** UCLA. Saturday.

February 9-10—**Sexual Therapy.** UCLA. Saturday-Sunday.

March 21-23—**Narcissism—A Multidimensional View.** UCSF. Friday-Sunday.

RADIOLOGY AND PATHOLOGY

October 18-20—**New Advances and Controversies in Neuroradiology.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. 17 hrs. $190.

October 18-21—**Society of Nuclear Medicine—4th Annual Western Regional Meeting.** See Medicine, October 18-21.

October 19-20—**Mycology Review** (a course for residents in dermatology and pathology). See Medicine, October 19-20.

November 2-4—**Radiology of the Gastrointestinal System (II).** American College of Radiology at San Francisco. Friday-Sunday. 15 hrs. $275. Contact: Maurice H. Trautz, Dir. of Ed., ACR, 6900 Wisconsin Ave., Chevy Chase, MD 20015. (301) 654-6900.

November 5—**American Association of Blood Banks—Annual Meeting.** Hilton Convention Center, Las Vegas. Monday. Contact: AABB, Suite 608, 1028 L St., NW, Washington, DC 20001.

November 12-14—**Liquid Chromatography in Clinical Analysis.** UCSF at Golden Gateway Holiday Inn, San Francisco. Monday-Wednesday. 19 hrs. $200.

January 9—**Gastrointestinal Radiology and Diagnosis.** LLU. Wednesday. 4 hrs.

January 23-26—**Clinical Obstetrics and Gynecology and Histological Pathology.** See Obstetrics and Gynecology, January 23-26.

January 25-27—**32nd Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Nathan Green, MD, 15107 Vanowen St., Van Nuys 91405.

January 26-27—**Modern Gastrointestinal Radiologic Techniques for Practicing Physicians.** UCSF at Fairmont, San Francisco. Saturday-Sunday. 13 hrs. $200.

January 28-February 1—**Computed Tomography, Ultrasound and X-Ray—An Integrated Approach.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. 32 hrs. $295.

January 30-February 1—**Genito-Urinary Pathology—7th Annual Course.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 22½ hrs. $220. Contact: Prog. Coord., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 1-3—**Neuroradiology.** UCSF at Fairmont, San Francisco. Friday-Sunday. 20 hrs. $190.

March 1-2—**Diagnostic Nuclear Imaging.** UCSF. Saturday-Sunday.

March 3-7—**Diagnostic Radiology.** UCSF. Monday-Friday.

March 8-9—**A Practical Course in B-Scan Ultrasound.** UCSF. Saturday-Sunday.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 23 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

October 19-20—**Cataract Surgery Pragmatics.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 16 hrs. $175. Contact: Program Coordinator. Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 585-3811.

October 28-November 9—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200, otolaryngologists; $900, residents. Contact: Antonio De La Cruz, MD, Ear Research Inst., 256 S. Lake St., Los Angeles 90057.

November 5-9—**American Academy of Ophthalmology.** Civic Auditorium, San Francisco. Monday-Friday. Contact: Faye Anderson, Dir. of Mtgs., P.O. Box 7424, San Francisco 94120. (415) 563-5725.

November 7—**Ridley 30 Year Anniversary Presentation.** American Intra-Ocular Implant Society at Brooks Hall, Civic Center, San Francisco. Wednesday. Contact: Debbi Miller, Dir. of Mtg. Services, A1O1S, P.O. Box 3140, Santa Monica 90403. (213) 395-3937.

November 9-10—**American Intra-Ocular Implant Society—6th Scientific Session.** Hyatt on Union Square, San Francisco. Friday-Saturday. 8 hrs. Contact: Debbi Miller, Dir. of Mtg. Services, A1O1S, P.O. Box 3140, Santa Monica 90403. (213) 395-3937.

November 24-December 1—**International Seminar on Operative Arthroscopy.** UCLA at Kauai, Hawaii. One week. 39 hrs. $650, with laboratories; $450 without laboratories.

December 6-8—**Trauma.** No. Calif. Chap. Committee on Trauma of the American College of Surgeons at Claremont Resort Hotel, Oakland. Thursday-Saturday. Contact: F. William Blaisdell, MD, Dept. of Surg., UCD Sch. of Med., Rm. 257, 4301 X St., Sacramento 95817. (916) 453-2207.

December 6-8—**Hand and Wrist Trauma.** The Bone and Joint Disease Foundation at San Diego. Thursday-Saturday. Contact: The Bone and Joint Disease Foundation, P.O. Box 82441, San Diego 92138.

December 6-9—**Gynecologic Urology.** See Obstetrics and Gynecology, December 6-9.

December 8—**Blepharoplasty and Other Cosmetic Surgery of the Eyelid.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

December 6-9—**Neurotology Workshop.** See Medicine, December 6-9.

January 14-18—**Otologic Surgery Course—15th Annual.** Ear Research Institute, Los Angeles. Monday-Friday. 40 hrs. $500. Contact F. H. Linthicum, Jr., MD, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

January 22-June 14—**Recent Advances in Surgical Science.** UCLA at Wadsworth VA Hospital, Los Angeles. One evening/month.

January 31-February 2—**Calculi.** American Urological Assn. at San Francisco. Wednesday-Friday. Contact: Office of Education, AUA, P.O. Box 1129, Aspen, CO 81611. (303) 925-2018.

February 6-8—**Annual Ophthalmology Course.** UCSF. Wednesday-Friday.

February 7-9—**Vascular Surgery.** UCSF. Thursday-Saturday.

February 8-9—**Cataract Surgery and Intraocular Lenses: Planned Extracapsular, Phacoemulsification and Intracapsular Techniques.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $450. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

February 14-15—**Head and Neck Trauma.** UCSF. Thursday-Friday.

March 1—**Corneal-External Ocular Disease Surgery Course.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $225. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

March 7-8—**Ophthalmology Update.** UCD, PMC, UCSF, STAN. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

March 9-11—**Plastic and Reconstructive Surgery.** UCSF. Sunday-Tuesday.

March 15-19—**Controversial Areas in Surgery—17th Annual Seminar.** UCLA at Canyon Hotel, Palm Springs. Saturday-Wednesday.

March 18-21—**Basic Science for Surgeons.** STAN at The Lodge, Pebble Beach. Tuesday-Friday.

March 19-23—**Vascular Surgery—8th Annual Symposium.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday.

March 25-29—**3rd U.S. Intraocular Lens Symposium and 7th Scientific Session.** American Intra-Ocular Implant Society at Century Plaza Hotel, Los Angeles. Tuesday-Saturday. 30 hrs. Contact: Debbi Miller, Dir. of Mtg. Services, AIOIS, P.O. Box 3140, Santa Monica 90403. (213) 395-3937.

OF INTEREST TO ALL PHYSICIANS

October 15-18—**Family Practice Update—4th Annual.** LLU. Monday-Thursday. 27 hrs. $200.

October 28-31—**California Academy of Family Physicians—Annual Scientific Assembly.** Masonic Auditorium, San Francisco. Sunday-Wednesday. Contact: CAFP, 9 First St., San Francisco 94105. (415) 982-6091.

November 1-3—**Postgraduate Institute on Human Sexuality.** CMA, UCD, UCLA, UCSF, UCSD, UCI at Erawan Gardens, Indian Wells. Contact: Charlotte Newhart, CMA.

November 2-4—**Physicians—Stress and Coping.** CMA and UCD at Pajaro Dunes, Watsonville. Friday-Sunday. 7 hrs. $75/person; $125/couple. Contact: Gail Jara, CMA.

November 3—**Exercise: Health Hazards and Benefits.** UCLA. Saturday. 5½ hrs. $85.

November 3, February 2, May 3—**Developmental Disabilities: Recent Developments and Trends.** See Psychiatry, November 3, February 2, May 3.

November 3-4—**Introductory Seminar on Medical-Dental Hypnosis.** San Diego and American Societies of Clinical Hypnosis at Honalei Hotel, San Diego. Saturday-Sunday. Contact: Ann M. Damsbo, PhD, 1062 W. 5th St., Escondido 92025. (714) 745-6640.

November 3-4—**Adaptation to Stressful Life Events.** UCSF. Saturday-Sunday. 12½ hrs. $80. Contact: UCSF, Cont. Ed. Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

November 4-7—**Southern Medical Association.** MGM Grand Hotel, Las Vegas. Sunday-Wednesday. In addition to 21 SMA programs, 22 postgraduate courses presented by AMA's Council on Cont. Physician Ed. Contact: SMA, 2601 Highland Ave., Birmingham, AL 35205.

November 5-9—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $290.

November 12-17—**American Society of Clinical Hypnosis—22nd Annual Scientific Meeting and Workshops.** San Francisco. Monday-Saturday. 40 hrs. $75, scientific program; $250, workshops. Contact: William F. Hoffman, Jr., Exec. Dir., 2400 E. Devon Ave., Suite 218, Des Plaines, IL 60018.

November 14—**Antibiotics.** LLU. Wednesday. 4 hrs.

November 16-17—**Nutrition in Your Daily Practice.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 17-18—**Third Annual Symposium on Aging.** UCSF. Saturday-Sunday. Contact: UCSF, Cont. Ed. Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

November 26-30—**Postgraduate Institute for Primary Care Physicians.** UCSD at Hilton Hotel, San Diego. Monday-Friday. 40 hrs.

November 30—**The Many Faces of Shock—1979.** Daniel Freeman Hospital at Hyatt House, Los Angeles. Friday. 6 hrs. $90. Contact: Donald A. Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Hosp., 333 N. Prairie Ave., Inglewood 90301. (213) 674-7050.

November 30-December 2—**Physicians—Stress and Coping.** CMA and UCD at Greenwood Lodge, Soquel. Friday-Sunday. 7 hrs. $75/person; $125/couple. Contact: Gail Jara, CMA.

December 1-2—**Sports Medicine Conference—9th Annual.** UCSF. Saturday-Sunday.

December 3-14—**Mental Retardation, Psychiatry and Primary Care.** See Psychiatry, December 3-14.

December 5-7—**Prevention in Primary Care.** UCSD at Vacation Village, San Diego. 20 hrs. $200.

December 9-11—**Nutritional Care of the Hospitalized Patient.** UCSF. Sunday-Tuesday.

December 14-16—**Critical Care Medicine: Taking Stock of Shock.** Medical Education Foundation of Santa Barbara County at Alisal Guest Ranch, Solvang. Friday-Sunday. 8 hrs. $65, members; $75, nonmembers. Contact: Tara Brown, MEF, 9 E. Pedregosa, Santa Barbara 93101. (805) 965-5275.

December 15—**Physical Assessment and Diagnosis Course for Emergency and Primary Care Physicians.** See Emergency Medicine, December 15.

January 8-March 25—**Clinical Acupuncture and Stimulation Produced Analgesia.** UCLA. Tuesday evenings.

January 12—**How to Get a Good Night's Sleep.** UCLA. Saturday.

January 12-13—**Current Drug Therapy in the Office.** UCLA. Saturday-Sunday.

January 21-25—**Therapy: Principles and Use of Drugs.** STAN at Hyatt on Union Square, San Francisco. Monday-Friday. 25 hrs. $290.

January 30-February 2—**Primary Care: Current Management of Common Office Problems.** UCSF. Wednesday-Friday.

February 1-7—**LLU Alumni Association—48th Annual Postgraduate Convention.** One week.

February 4-9—**Family Practice Refresher Course—11th Annual.** UCI at Marriott Inn, Newport Beach. Monday-Saturday.

February 7-13—**California Medical Association—109th Annual Session.** Town and Country, San Diego. Thursday-Wednesday. Contact: Rocki Lai, CMA.

February 9-10—**Sexual Therapy.** See Psychiatry, February 9-10.

February 14-15—**Management of the Ventilator Dependent Patient.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. 14 hrs. Contact: Prog. Coord., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 14-16—**Medicine and the Changing World.** Vista Hill Foundation at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Virginia Everett, Vista Hill Fnd., 7798 Starling Dr., San Diego 92123. (714) 278-6761.

February 24-26—**Neurology for Non-Neurologists.** UCSD at Hilton, San Diego. Sunday-Tuesday. 21 hrs. $250.

February 25-29—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $290.

February 26-March 2—**Critical Care Medicine.** USC at Hilton, San Francisco. Tuesday-Sunday.

February 27—**Hospital Infection Control.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday. 7 hrs. Contact: Prog. Coord., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

March 1-2—**Genetic Disorders.** UCLA. Saturday-Sunday.

March 15, 29—**Placebos: The Power of Positive Expectant Faith.** UCLA. 2 Saturdays.

March 18-22—**Sports Medicine.** University of Hawaii School of Medicine at Princess Kaiulani Hotel, Waikiki, Honolulu, Hawaii. Tuesday-Saturday. 18 hrs. $200. Contact: Hawaii Conference Services, P.O. Box 25055, Honolulu 96825. (808) 377-6445.

March 24-28—**Postgraduate Institute for Primary Care Physicians.** UCSD at Vacation Village, San Diego. Monday-Friday.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland, OR 97227. (503) 280-3200.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

February 11-15—**Eleventh Annual Family Practice Review.** Portland, Monday-Friday. Hilton Hotel. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OBSTETRICS AND GYNECOLOGY

October 22-24—**Third Annual Pacific Northwest Review of Obstetrics and Gynecology.** Portland, Monday-Wednesday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

SURGERY

December 7-8—**Recent Advances in Surgery.** Portland, Friday-Saturday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OF INTEREST TO ALL PHYSICIANS

November 1-2—**Oregon Medical Association 105th Annual Scientific Assembly.** Red Lion Motor Inn, Portland Center, and OMA Headquarters, Portland. Contact: Sondra Gleason, Oregon Medical Association, 5210 SW Corbett Avenue, Portland, OR 97201. (503) 226-1555. (See editorial page 352 in this issue for details.)

November 16-17—**Sixth Annual Symposium on Critical Care Medicine.** Portland, Friday-Saturday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 16-20—**American College of Physicians Review Course.** Portland, Monday-Friday. Jantzen Beach Thunderbird. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 25-27—**Symposium on Sports Medicine.** Eugene, Wednesday-Friday. Thunderbird Motor Inn. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

October 18-19—**Thyroid Disorders and Treatment.** Port Ludlow. Thursday-Friday. Port Ludlow Resort. Contact: Marlyn Carlson, Northwest Hospital, 1551 N 120th, Seattle, WA 98133. (206) 364-0500, ext. 686.

October 19-20—**Nutrition for Physicians.** Seattle. Friday-Saturday. U/W Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

November 1-2—**Controversies in Critical Care Medicine.** Spokane. Thursday-Friday. Red Lion Motor Inn. Contact: Debbie Shirley, RN, E. 8617 Upriver Drive, Spokane, WA 99206. (509) 928-9205.

November 1-2—**Drug Therapy.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

November 2-3—**Urology for the Generalist.** Seattle. Friday-Saturday. Swedish Hospital and Medical Center. Contact: John L. Wright, MD, Swedish Hospital and Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2265.

November 3—**Infectious Diseases.** Tacoma. Saturday. Tacoma General Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

November 4-7—**Twenty-Two Postgraduate Courses.** Las Vegas, Nevada. Sunday thru Wednesday. Contact: AMA Department of Meeting Services, 535 North Dearborn Street, Chicago, Illinois 60610.

November 7—**Endocrinology Circuit Course.** Seattle. Wednesday (4 hours). Ballard Community Hospital, Seattle. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

November 8-9—**Basic Psychotherapeutic Techniques.** Seattle. Thursday-Friday. Swedish Hospital Auditorium. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

November 10-11—**Biofeedback in Clinical Practice.** Tacoma. Saturday-Sunday. University of Puget Sound. Contact: Dorothy Woods, Washington State Physical Therapists Association, 5426 119th Ave., S.E., Bellevue, WA 98006. (206) 746-2595.

November 15-16—**Critically Ill Surgical Patient.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

November 15-17—**Pearls in Primary and Emergent Care.** Seattle. Thursday-Saturday. Washington Plaza Hotel. Contact: Marilyn Carlson, Northwest Hospital, 1551 North 120th, Seattle, WA 98133. (206) 364-0500, ext. 686.

November 17-24—**Tax Estate and Financial Planning.** Kauai, Hawaii. Saturday thru Saturday. Kauai Surf. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

November 28—**Endocrinology Circuit Course.** Spokane. Wednesday (4 hours). Sacred Heart Medical Center, Spokane. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

November 30, December 1—**Aging and the Elderly.** Seattle. Friday-Saturday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

December 1-2—**Dynamics of Patient-Physician Relationships.** Seattle. Saturday-Sunday. 6th Floor, Group Health Cooperative of Puget Sound. Contact: Office of Education, Group Health, A-5, 201 16th Ave., E., Seattle, WA 98112. (206) 326-7348.

December 6-7—**American College of Physicians MKSAP V.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

December 6—**Behavioral Methods in Pain Management.** Seattle. Thursday. Swedish Hospital Auditorium. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

December 7—**Biofeedback.** Seattle. Friday. Swedish Hospital Auditorium. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

December 14-15—**Orthopedics for the Family Physician.** Seattle. Friday-Saturday. Swedish Hospital and Medical Center. Contact: John L. Wright, MD, Swedish Hospital and Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2265.

January 12—**Conference on Obstetrics and Gynecology.** Seattle. Saturday. Providence Medical Center. Contact: Evelyn Foote, Continuing Education, Providence Medical Center, 500 17th Ave., Seattle, WA 98122. (206) 326-5821.

January 17-18—**Pediatric Update.** Seattle. Thursday-Friday. Children's Orthopedic Hospital and Medical Center. Contact: UW School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

January 23-February 1—**Critical Care I and Ski.** Val Gardenia, Italian Alps. Ten Days. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

January 26—**Radiology Above the Belt.** Seattle. Saturday. 6th Floor, Group Health Cooperative of Puget Sound. Contact: Office of Education, Group Health, A-5, 201 16th Ave., E., Seattle, WA 98112. (206) 326-7348.

January 26—**Rheumatology.** Tacoma. Saturday. St. Joseph Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

January 29-30—**Tax Estate and Financial Planning.** Seattle. Tuesday-Wednesday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 1-2—**Violence in the Family.** Seattle. Friday-Saturday. Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 9-16—**Sun Valley Critical Care: Maternal/Perinatal.** Sun Valley, Idaho. Saturday thru Saturday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 14-15—**Advances in Neurology: Headaches.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 15—**Peripheral Vascular Disease.** Tacoma. Friday. Tacoma General Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

February 18—**Endocrinology Circuit Course.** Vancouver, WA. Monday (4 hours). St. Joseph Community Hospital. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 19—**Endocrinology Circuit Course.** Longview. Tuesday (4 hours). Monticello Medical Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 20—**Endocrinology Circuit Course.** Olympia. Wednesday (4 hours). Tyee Motor Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 21—**Endocrinology Circuit Course.** Bremerton. Thursday. Harrison Memorial Hospital. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 22—**Endocrinology Circuit Course.** Bellingham. Friday. Western Washington University. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 23-March 1—**Office Orthopedics for Primary Physicians.** Sun Valley, Idaho. Saturday-Saturday. Sun Valley Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 28-29—**Northwest Stroke Symposium.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: Education and Training Department, Northwest Hospital, 1551 North 120th Seattle, WA 98133. (206) 364-0500, ext. 686.

March 6-7—**American College of Physicians Medical Knowledge Self-Assessment Program V (MKSAP V).** Seattle. Thurs

day-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 8-15—**Psychiatry for Primary Physicians.** Sun Valley, Idaho. Saturday-Saturday. Sun Valley Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 9-15—**Critical Care II and Ski.** Lake Tahoe. Thursday-Wednesday. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

March 13-14—**Tacoma Academy of Internal Medicine Annual Scientific Program.** Tacoma. Thursday-Friday. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

March 15-22—**Sports Medicine.** Sun Valley, Idaho. Saturday-Saturday. Sun Valley Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 17-28—**Rehabilitation Medicine Review.** Seattle. Two weeks. University Towers Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 21-22—**Days of Pediatrics.** Tacoma. Friday-Saturday. Mary Bridge Children's Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98450. (206) 627-7137.

March 24-28—**Advances in Family Practice.** Seattle. Monday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 29-April 5—**Infectious Diseases.** Hilo, Hawaii. Saturday-Saturday. Naniloa and Kona Surf Hotels. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 31-April 3—**American College of Physicians: Hematology.** Seattle. Monday-Thursday. Olympic Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 3-4—**Hazards to the Fetus.** Seattle. Thursday-Friday. Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 10-11—**Dermatology.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 10-11—**Annual Cancer Symposium—Gastrointestinal.** Seattle. Thursday-Friday. Swedish Hospital and Medical Center. Contact: John L. Wright, MD, Swedish Hospital and Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2265.

April 17-18—**Couples.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 18-19—**Tacoma Surgical Society Annual Scientific Program.** Tacoma. Friday-Saturday. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

April 24-25—**Respiratory Care.** Seattle. Thursday-Friday. Contract: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 24-25—**Review of Arrythmias.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 25-26—**Anesthesia: Low Flow States—Pathology and Treatment.** Vancouver, British Columbia. Friday-Saturday. Four Seasons Hotel. Contact: Dr. K. Turnbull, Academy of Medicine, 1807 West 10th Avenue, Vancouver, BC V6J 2A9.

May 1-2—**Controversies in Medicine.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 22-23—**Adolescent Medicine.** Seattle. Thursday-Friday. Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 5—**Medicine and the Law.** Port Ludlow. Thursday. Port Ludlow Resort. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 12-13—**Regional Anesthesia and Nerve Block.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 19-20—**Laboratory Medicine.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 26-27—**American College of Physicians Medical Knowledge Self-Assessment Program V (MKSAP V).** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 28-July 5—**Alaska Cruise—Emergency Medical Care: Trauma, Orthopedics and Surgery; Biomedical History.** 8 days. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

July 13-20—**Alaska Cruise—Emergency Medical Care: Trauma, Orthopedics and Surgery; Biomedical History.** 8 days. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

November 1—**Depression and Manic Depression—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 45th, Anchorage, AK 99023. (907) 274-7579.

November 28—**Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

MONTANA

October 24-26—**Transient Ischemic Attack and Stroke—Univ. of Wash. Internal Medicine Review Sessions.**

October 24, Wednesday, Great Falls. 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

October 25, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

October 26, Friday, Missoula. 8:30-11 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

November 14-16—**Prostaglandins—Univ. of Wash. Internal Medicine Review Sessions.**

November 14, Wednesday, Great Falls. 4:30-7:30 p.m. Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

November 15, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

November 16, Friday, Missoula. 8:30-11 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

November 28—**Pediatric Surgery—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner,

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: 1980—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 23-27, 1980, Registry Resort, Scottsdale.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: February 7-13, 1980, Town and Country, San Diego.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: 1980—date and place to be announced.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: 1980—date and place to be announced.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1980, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: 1980—date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 16-18, 1980, MGM Grand, Las Vegas.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 7-9, 1980, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 SW Corbett Ave., Portland 97201. Annual Scientific Meeting: November 1-2, 1979, Red Lion Inn, Portland Center, Portland.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: 1980—date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: 1980—date and place to be announced.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 23-27, 1980, Snow King Inn, Jackson.

MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

December 12—**Genetics—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

December 12-14—**ENT for Internists—Univ. of Wash. Internal Medicine Review Sessions.**

December 12, Wednesday, Great Falls. 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

December 13, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

December 14, Missoula. 8:30-11 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

IDAHO

October 15—**Premature Labor—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391.

October 23—**Pediatric Hematology—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

November 19—**Prenatal Diagnosis—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391.

November 27—**Pediatric Radiology—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

December 11—**Pediatric Infectious Diseases—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

February 9-16—**Sun Valley Critical Care: Maternal/Perinatal.** Sun Valley, Idaho. Saturday thru Saturday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

Index to
The Western Journal of Medicine Advertising

BANK OF AMERICA
Business Services 31
BETH ISRAEL CONFERENCE PROGRAM
1980 Winter Schedule 29
BOEHRINGER INGELHEIM LTD.
Catapres 9, 10, 11, 12
BURROUGHS WELLCOME CO.
Zyloprim 2
CALIFORNIA MEDICAL ASSOCIATION
109th Annual Session 26
CHILDRENS HOSPITAL OF LOS ANGELES
Annual Fall Alumni Program 32
CLASSIFIED 30, 32, 34
DOCTORS' COMPANY, THE 7
ELI LILLY AND COMPANY
Keflex 6
FIRSTMARK CAPITAL CORPORATION 2
HAWAII UNIVERSITY
Sports Medicine Course 29
LOS ANGELES RADIOLOGICAL SOCIETY
Midwinter Radiological Conference for 1980 35
MERCK SHARP & DOHME
Aldoril 16
NORTHWEST HOSPITAL
Stroke Symposium 34
OBETROL PHARMACEUTICALS
Obetrol 8
ORTHO PHARMACEUTICALS
Monistat IV 18, 19, 20
INTERNATIONAL MEDICAL EDUCATION CORPORATION
Medical Educational Programs 24
PHARMACEUTICAL MANUFACTURERS ASSOCIATION 22, 23
PHYSICIANS & SURGEONS INSURANCE EXCHANGE 33
PUREPAC PHARMACEUTICAL CO. 17
PVO INTERNATIONAL
Saffola Margarine 21
ROCHE LABORATORIES
Gantanol ..... 2nd Cover, 1, 2
Valium ..... 3rd & 4th Covers
SANDOZ PHARMACEUTICALS
Hydergine 5
SMITH KLINE & FRENCH COMPANY
Tagamet 3
E. R. SQUIBB & SONS, INC.
Halog 27, 28, 29
UNITED CALIFORNIA BANK 25
UPJOHN COMPANY, THE
Motrin 13, 14, 15, 16

THE WESTERN Journal of Medicine

VOLUME 131 • NUMBER 5 **NOVEMBER 1979**

355 *New Techniques in the Evaluation of Cerebrovascular Disease*
STANLEY N. CARSON, MD, and F. WILLIAM BLAISDELL, MD

364 *Adriamycin (Doxorubicin) Cardiotoxicity: A Review* ROWAN T. CHLEBOWSKI, MD, PhD

369 *The Epidemiology of Thyroid Cancer in Los Angeles County*
SUSAN PRESTON-MARTIN, PhD, and HERMAN R. MENCK, MBA

MEDICAL PROGRESS

373 *The Clinical Physiology of Water Metabolism—Part I: The Physiologic Regulation of Arginine Vasopressin Secretion and Thirst*
RICHARD E. WEITZMAN, MD, and CHARLES R. KLEEMAN, MD

SPECIALTY CONFERENCE

401 *Symposium on Adolescent Gynecology and Endocrinology—Part I: Physiology of Sexual Maturation and Primary Amenorrhea*
Moderators: GLENN D. BRAUNSTEIN, MD, and WILLIAM D. ODELL, MD, PhD; Discussants: WILLIAM D. ODELL, MD, PhD, and DANIEL D. FEDERMAN, MD
A Symposium held at the 26th Annual Meeting of the Pacific Coast Fertility Society, Scottsdale, Arizona

MEDICAL STAFF CONFERENCE

417 *Cimetidine* Chief Discussant: BRUCE SCHARSCHMIDT, MD

IMPORTANT ADVANCES IN CLINICAL MEDICINE

426 *Neurosurgery—Epitomes of Progress*

EDITORIALS

433 • *PSRO, Politics and Quality Assurance* • *Noninvasive Evaluation of Cerebrovascular Disease* • *Planning for Health Manpower* • *Water Homeostasis—Facts and Uncertainties*

CASE REPORTS

438 *Meningitis Caused by Group II J Following a Dog Bite*
RAYMOND BRACIS, MD; KATHY SEIBERS, MT, and ROBERT M. JULIEN, MD, PhD

440 *Psoriatic Arthritis Induced by Varicella* LINDA SKORY, MD, and MARTIN A. SHEARN, MD

441 *The Athletic Heart Revisited—Sudden Death of a 28-Year-Old Athlete*
LCDR SANFORD E. WARREN, MC, USNR; LT JAMES B. BOICE, MC, USNR; COLIN BLOOR, MD, and CAPT W. V. R. VIEWEG, MC, USN

CORRESPONDENCE

448 • *Irish Spring Soap* • *Primary Hypertension—A Disease Entity?* • *Of Decibels, 'Highs' and Privacy* • *Clonidine Withdrawal—Fact or Fiction?; With Reply by Author*

INFORMED OPINION

451 *Perceptions on PSRO* ALAN R. NELSON, MD

CONTROVERSIAL ISSUES IN MEDICINE

455 *Changing Attitudes Toward Abortion* MALCOLM POTTS, MB, BChir, PhD

462 *In Memoriam*

Books Received, See Advertising Page 24

11M92-021 791102NEWENGLAJ001
NEW ENGLAND JOURNAL OF MED
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★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII; OREGON; WASHINGTON; ALASKA, MONTANA AND IDAHO**
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- the potent antispasmodic-antimotility actions of QUARZAN® (clidinium Br/Roche)

Adjunctive

LIBRAX®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

A distinct advantage for patients with irritable bowel syndrome

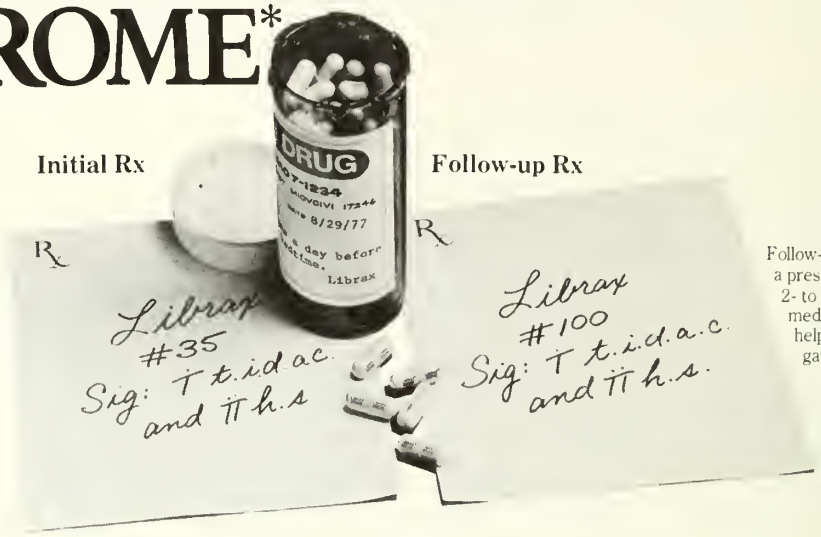
ROCHE

*Librax has been evaluated as possibly effective for this indication. Please see brief summary of prescribing information on following page.

A DISTINCT ADVANTAGE FOR PATIENTS WITH IRRITABLE BOWEL SYNDROME*

Initial Rx

The initial prescription allows evaluation of patient response to therapy.



Follow-up Rx

Follow-up therapy with a prescription for a 2- to 3-week supply of medication usually helps maintain patient gains.

Adjunctive

LIBRAX®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

antianxiety/antispasmodic/antimotility

Please consult complete prescribing information, a summary of which follows:

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl/Roche) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated, avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

How Supplied: Available in green capsules, each containing 5 mg chlordiazepoxide HCl (Librium®) and 2.5 mg clidinium Br (Quarzan®)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.

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work/play—normal hemodynamic responses to exercise maintained.

love—low incidence of impotence and/or loss of libido: 2.8% in 1,923 patients studied.[1]

cardiac output—tends to return to control values during long-term therapy.

blood flow—preserved in kidney.

No Single Advantage Determines Drug Choice.

Other factors must include:

The drug's effectiveness in a given patient, its side effects, warnings, precautions, tolerance, etc. A rational therapeutic choice depends on a careful assessment of all such factors.

*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

1. Data on file at Boehringer Ingelheim Ltd.

Please see last page for brief summary, including warnings, precautions, and adverse reactions.

Tablets of 0.1 mg and 0.2 mg

Catapres®

(clonidine HCl)

HYPERTENSION

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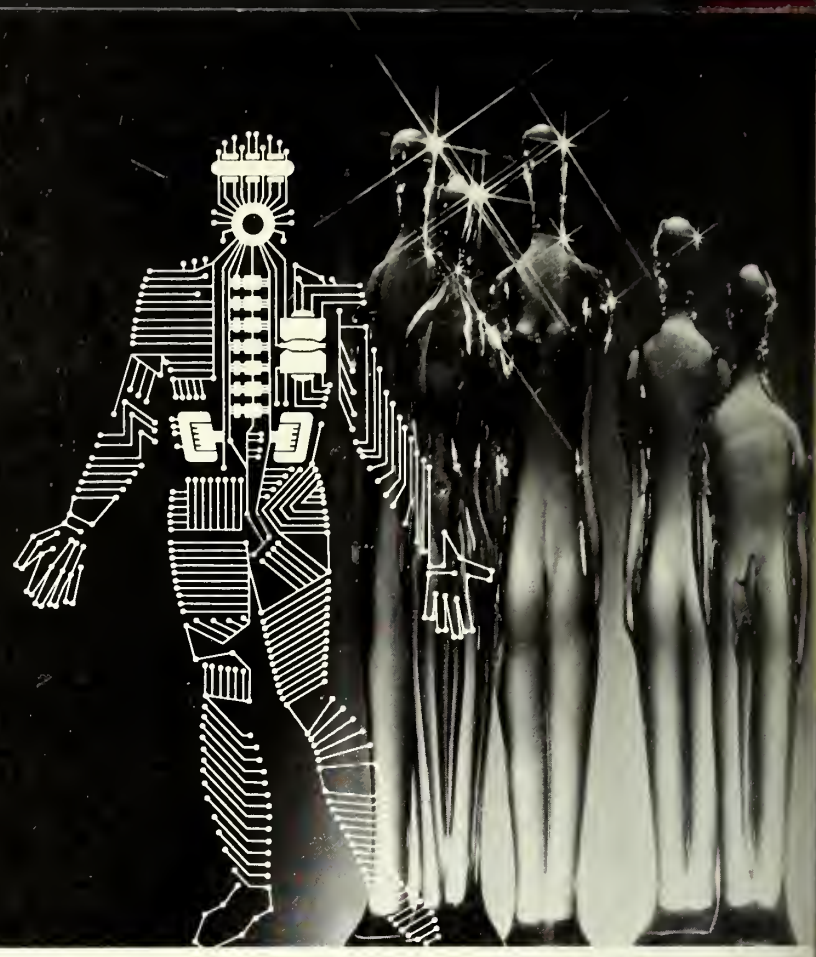

- No contraindications.
- Effective in all degrees of hypertension. It is mild to moderate in potency.
- Low incidence of depression, impotence, orthostatic hypotension—no fatal hepatotoxicity.
- Preserves kidney blood flow.

Most common side effects are dry mouth, drowsiness, and sedation which generally tend to diminish with time.

The usual starting dose of Catapres is 0.1 mg at breal fast and 0.1 mg at bedtime. Some patients may benef from a starting dose of 0.1 mg at bedtime.

Usual daily dose range—0.2—0.8 mg

Maximum daily dose—2.4 mg (12 tablets of 0.2 mg). Doses as high as this have rarely been employed.

For optimal results, the dose of Catapres must be adjusted according to the patient's individual blood pressure response.

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 mon longer.

Adverse Reactions: The most common reactions are dry mouth, drowsines sedation. Constipation, dizziness, headache, and fatigue have been rep Generally these effects tend to diminish with continued therapy. The follo reactions have been associated with the drug, some of them rarely. (In instances an exact causal relationship has not been established.) These inc Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalit liver function tests; one report of possible drug-induced hepatitis without ic and hyperbilirubinemia in a patient receiving clonidine hydrochloride, thalidone and papaverine hydrochloride. Weight gain, transient elevation of glucose, or serum creatine phosphokinase: congestive heart failure, Rayn phenomenon; vivid dreams or nightmares, insomnia, other behavioral cha nervousness, restlessness, anxiety and mental depression. Also rash gioneurotic edema, hives, urticaria, thinning of the hair, pruritus not asso with a rash, impotence, urinary retention, increased sensitivity to alcohol, dry itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecom weakly positive Coombs' test, asymptomatic electrocardiographic abnorm manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished sent reflexes and vomiting followed the accidental ingestion of Catapres (clo hydrochloride) by several children from 19 months to 5 years of age. G lavage and administration of an analeptic and vasopressor led to comple covery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-m intervals usually abolishes all effects of Catapres, (clonidine hydrochloride) dosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and

For complete details, please see full prescribing information.
Under license from Boehringer Ingelheim GmbH

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brand of

cimetidine

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in single-dose vials
and in 8 ml. multiple-dose vials,
both in packages of 10.

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The Maker

Examining a Few Myths About Prescribing.

Increasing pressure is being put on the practicing physician to prescribe drugs generically. You are told that brand–name products are universally "expensive" and generic versions are relatively "cheap." To make this case, the most extreme (rather than typical) price differentials are cited. Thus, consumers are led to believe that such differentials are commonplace. Even your knowledge and your motives as a physician are questioned.

Understandably, these views have created myths. We think it's time to examine them in the light of all the facts and ramifications.

MYTH: There are no differences in quality and performance between brand-name products and their generic counterparts. The corollary is that there are no differences among products made by high-technology, quality-conscious, research-based companies and those made by commodity-type suppliers.

FACT: The Food and Drug Administration does a good job in monitoring a generally excellent drug supply. Still, it has nowhere near the resources to guarantee the quality and bioavailability of all marketed products at any given time. Just a few months ago, for example, it noted that batches of tetracycline HCl capsules which met official monograph requirements were not bioequivalent to a reference product. As you know, there is substantial literature on this subject affecting many drugs, including such antibiotics as tetracycline and erythromycin. The record on drug recalls and court actions affirms strongly that there are differences among pharmaceutical companies and their products. Research-intensive companies have far better records than those that do no research and may practice minimum quality assurance.

MYTH: Industry favors only "expensive" brand names and denigrates all generics.

FACT: PMA companies make 90 to 95 percent of the drug supply, including, therefore, most of the generics. Drug nomenclature is not the important point; it's the competence of the manufacturer and the integrity of the product that count.

Matters.

MYTH: Generic options almost always exist.

FACT: About 55 percent of prescription drug expenditure is for single-source drugs. This means, of course, that for only 45 percent of such expenditure, is a generic prescribing option available.

MYTH: Generic prescriptions are filled with inexpensive generics, thus saving consumers large sums of money.

FACT: Market data show that you invariably prescribe—and pharmacists dispense—both brand and generically labeled products from known and trusted sources, in the best interest of patients. In most cases the patient receives a proven brand product. Savings from voluntary or mandated generic prescribing are grossly exaggerated.

MYTH: Drugs account for a major portion of the rise in health care costs.

FACT: Drugs represent a very small part of such costs. The amount of the health care dollar spent for prescription drugs was about 12 cents in 1967; today it is about 8 cents. And you as a physician are most conscious of how drug therapy can cut hospitalization, avert surgery, reduce office visits and keep patients on the job.

MYTH: Government intrusions into the marketplace will save tax money.

FACT: Government schemes always cost the taxpayer something, and the costs often exceed the benefits. Certainly, any federal "help," such as lists of wholesale drug prices sent to all physicians and pharmacists, will be no exception. Just think of the expense of keeping them current! Moreover, wholesale prices are poor guides to actual transaction prices and even worse guides to retail prices.

The PMA Position

We believe your freedom to prescribe, either by generic or brand name, should be totally unabridged. Otherwise, your prescribing prerogatives and your relationships with patients will be seriously impaired.

The maker does matter

After the myths about price and equivalency have been shattered, one fact stands out more clearly than ever: *The maker does matter.* As always, your best guide to drug therapy for your patients is to select products—both brands and generics—from manufacturers with credentials and performance records you have come to respect.

PMA

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
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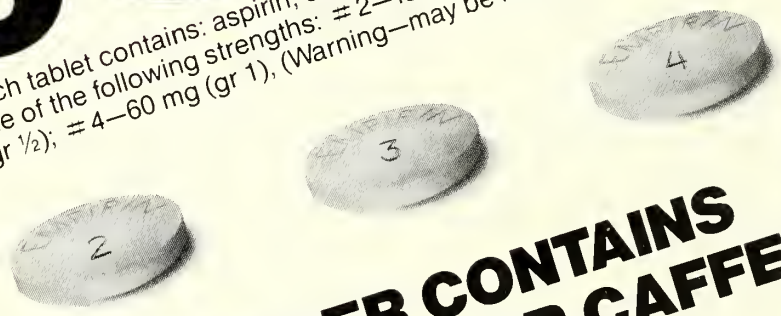

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They're in their late sixties, the beneficiaries of more liberal retirement laws and more enlightened attitudes toward the elderly. They're leading socially productive lives. But recently, without any clear cause, they had each begun to experience mild episodes of symptoms such as confusion, mood-depression, and dizziness. Their ability to function could have been jeopardized. That's when they became the beneficiaries of oral Hydergine therapy.

The still-functioning geriatric can benefit from Hydergine treatment

It is quite common for cognitive and emotional symptoms of deterioration to manifest gradually in the elderly. During this early stage, such symptoms are mild and more amenable to treatment. It is at this stage that Hydergine therapy has proved most effective. Patients tend to respond better, and with symptoms effectively relieved—or at least their progression retarded—the ability to function can be maintained.

Oral Hydergine tablets promote better patient compliance

Compared with the sublingual form, dosage administration is easier, with less need for supervision.

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Contraindications: Hypersensitivity to the drug.
Precautions: *Because the target symptoms are of unknown etiology, careful diagnosis should be attempted before prescribing Hydergine tablets and sublingual tablets.*
Adverse Reactions: Serious side effects have not been found. Some sublingual irritation, transient nausea, and gastric disturbances have been reported. Hydergine tablets and sublingual tablets do not possess the vasoconstrictor properties of natural ergot alkaloids.
Dosage and Administration: 1 mg three times daily. Alleviation of symptoms is usually gradual and results may not be observed for 3–4 weeks.
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New Techniques in the Evaluation of Cerebrovascular Disease

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Numerous reports in the literature indicate that various noninvasive vascular techniques can now be used to evaluate atherosclerosis at the carotid bifurcation. This article reviews noninvasive screening techniques currently available and being developed. Particular emphasis has been placed on the practicality of these techniques as well as their limitations. Our conclusions are that noninvasive techniques cannot be used as definitive screening tests for cerebrovascular disease. Although these tests are frequently useful when positive, the false negative rate of these tests would appear to be significant and variable in different hands. Nonstenotic ulcers are usually not detected and total occlusion often not differentiated from stenosis. These tests should be viewed as the beginning rather than the end result of a developing field. At present, contrast arteriography remains the definitive test to evaluate the presence and significance of extracranial cerebrovascular disease.

THERE ARE MANY PROCEDURES available for assessing cerebrovascular disease noninvasively. Each has its distinct advantages and disadvantages. There are also some new procedures emerging which may offer great potential towards the goal of screening outpatients in whom angiography may or may not be needed.

The purpose of this article is to review currently available testing procedures and their results. We also will discuss some of the techniques in development which are not yet available for general use.

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The Doppler Cerebrovascular Examination

The Doppler examination is the commonest technique now used for screening in cases of cerebrovascular disease.

Theory

Blood flow through the internal carotid artery is distributed entirely to the intracranial vessels with the exception of the ophthalmic artery. The ophthalmic artery before terminating in the retinal artery supplies the nasal, supraorbital and frontal branches to the face (Figure 1). The frontal and supraorbital branches turn upward and communicate with the external carotid artery through the superficial temporal artery. The nasal artery turns downward and becomes the angular artery communicating with the facial branch of the external

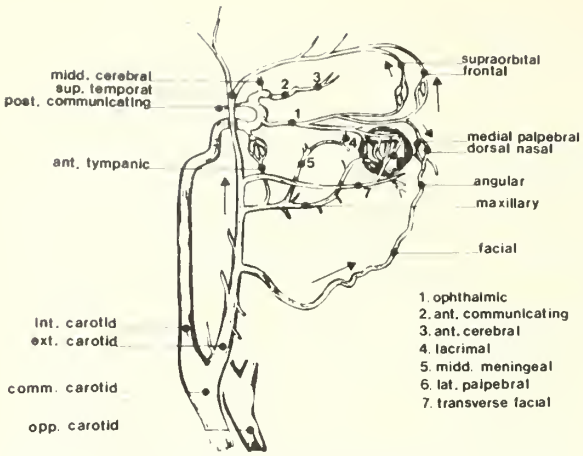

Figure 1.—Diagram showing collateralization between external and internal carotid circulations. Supraorbital, frontal, superficial temporal and facial arteries are key in the Doppler examination of carotid circulation. (Reproduced with permission from Spencer MP, et al: Non-Invasive Cerebrovascular Evaluation [training manual]. Seattle, Institute of Applied Physiology and Medicine.)

carotid artery. Other communications between the intracerebral and extracerebral circulation occur through lacrimal and ethmoid branches. Periorbital arteries may also anastomose with the contralateral periorbital arteries. In the periorbital arteries flow normally proceeds from the internal carotid to its junction with larger vessels of the external carotid artery. Abnormal flow direction or suppression can mean internal carotid artery stenosis.

Other collateral channels occur intracranially via the circle of Willis. The anterior communicating artery provides collateral intercerebral circulation from the opposite carotid artery. The posterior communicating artery provides collateral communication between the carotid arteries and the vertebral arteries.

Technique

The directional Doppler probe is placed over the periorbital branches of the internal carotid artery usually the supraorbital, frontal or nasal branches. It is noteworthy that the angular artery is often absent. A recording can be made and direction of flow is noted. Reversal of direction indicates stenosis of the ipsilateral internal carotid artery has occurred. The superficial temporal artery is then compressed. This normally should give no change or produce augmentation of the supraorbital or frontal artery signals. Diminished or obliterated signals in the periorbital branches following compression of the superficial temporal artery means abnormal retrograde flow secondary to internal carotid stenosis.

The facial artery is also compressed and its similar effect on the Doppler signal from the frontal artery is noted. Common carotid compression is then carried out for one to two heartbeats; ipsilateral compression diminishes flow in the periorbital vessels and contralateral compression normally has no effect. If contralateral carotid compression shows decreased flow it is assumed to be a collateral for the ipsilateral internal carotid circulation and therefore ipsilateral stenosis exists. The test is then repeated on the contralateral side of the face.

A carotid stenosis of 75 percent in diameter which leaves a lumen of less than 2.5 mm in diameter *usually must exist* for these tests to be positive. The most reliable signs of collateralization, and therefore stenosis, are abnormal direction of flow and evidence of crossover flow from the opposite carotid artery. Asymmetry and dampened signals are suspicious only. Some Doppler techniques call for listening directly through the eye to the ophthalmic artery.

Experience

Bone and Barnes[1] reviewed the cases of 56 patients with hemispheric transient ischemic attacks (TIA's) or resolved hemispheric stroke. They describe listening to the frontal artery and compressing the infraorbital, facial and superficial temporal arteries, and both carotid arteries. They previously reported 453 examinations with a 99 percent diagnostic accuracy if the stenosis was 75 percent or greater. Of the above 56 patients, 36 had lesions amenable to endarterectomy and 7 had complete occlusions. The overall accuracy of the Doppler examination was reported to be 94 percent in identifying lesions over 75 percent stenotic. However, it is noted in these figures that seven of 18 of the patients with over 75 percent stenosis had complete occlusion with a 100 percent accuracy in Doppler detection. Of the remaining 11 the stenosis was diagnosed in 10, or 91 percent accuracy. The accuracy in operable stenosis under 75 percent was only 31 percent with a high false negative rate. Stenosis could not be differentiated from occlusion.

In a further report on patients evaluated by Doppler assessment of supraorbital artery flow, Barnes and co-workers[3] describe increasing the

accuracy from 64 percent to 68.7 percent when internal carotid artery stenosis was over 50 percent by assessing frontal artery flow in addition to temporal artery flow. The authors emphasized that about two thirds of their patients with significant extracranial carotid lesions presumed responsible for symptoms had a stenosis of less than 50 percent on angiography and this would have been overlooked by the screening procedure.

Lye and co-workers[4] reported the cases of 50 patients who had undergone 102 carotid Doppler examinations. Of these patients, 32 had TIA's, 12 had cerebrovascular accidents (CVA's) and 6 had asymptomatic bruits. The supraorbital artery was evaluated and superficial temporal artery compression was carried out. False positive Doppler results were 1 percent to 2 percent, false negatives were 22 percent. They found that Doppler examinations were more likely to be positive when a bruit was present when results were compared with angiography. These investigators found that most false positives were due to common carotid lesions, ipsilateral internal carotid artery lesions, external carotid occlusion or a presumed anterior communicating artery which provided abundant collateral flow.

Brockenbrough, who originally described this technique, initially reported 2 percent false negative and 3 percent false positive results in 124 examinations.[5] Later he reported 17/19 correlations with angiography if stenosis was over 50 percent and 2/51 correlations if stenosis was less than 50 percent.[6]

A report by Moore and associates dealt with 152 patients who had undergone 304 carotid studies.[7] In the first 72 patients the supraorbital branch was evaluated with superficial temporal artery compression. In the last 80 patients relationships between facial and frontal arteries were also evaluated. The patient population is not well characterized but apparently some were asymptomatic. An 86 percent overall accuracy rate is described with 94 percent being obtained in the latter part of the series. This paper differs from other series because of a lack of any significant false negatives. Since the patient population is not described it seems possible that this may represent an arteriographically screened population all of whom had lesions. The discussion following this report is notable because the authors report their accuracy was increased by the addition of the frontal-facial study.

Finally, McDonald and co-workers have reported 3 percent false positives, 24 percent false negatives and 74 percent accuracy for the Doppler cerebrovascular examination at Walter Reed Army Hospital.[8]

The complete examination as described has been done in 98 angiogramed carotids (49 patients) at Martinez Veterans Administration Medical Center. All patients had symptoms referable to cerebrovascular disease (40 hemispheric TIA's or amaurosis fugax and nine post-cerebrovascular accidents). The false negative rate was approximately 20 percent. This appears to be due to bilateral stenosis, stenosis at the bifurcation and presumed efficient intracerebral collaterals.

Comment

Not all investigators do the thorough examination discussed above and this may be one reason for varying results reported in the literature. Many examiners also include diminished flow as a definitive indication of carotid stenosis. The high rate of false negatives with this technique is worrisome since all the series reported above represented selected populations. Nonstenotic ulcers, in particular, are not detected. Variance in result from technician to technician has been frequent in our experience and it can be very difficult to find prominent supraorbital branches; when found they are often tortuous.

Our conclusions regarding this practical and commonly used procedure is that the Doppler probe is the least expensive and probably from this standpoint the most practical of all tests described herein. An excellent directional Doppler probe can be purchased for $850 and a nondirectional one for $300 (Parks Electronic Co., Beaverton, Oregon). If the test is positive, it is most often significant but stenosis versus total occlusion is not usually differentiated.

It should not by itself be used for a screening test unless definitely positive because of the high rate of false negatives and lack of reported use in a prospective population survey.

Supraorbital Photoplethysmography

Theory

A transducer transmits infrared light into tissues with reflections from blood being recorded as pulsatile flow. The amount of the reflection can be qualitatively recorded and is proportional

to the amount of flow. The transducers are placed over the medial aspect of each supraorbital area and compressions carried out as with Doppler examinations. Direction of flow cannot be determined.

Experience

Barnes and co-workers[9] reported on the examination in 156 vessels of 78 patients. Although the patient population was not well described, it is stated that this test had an overall accuracy rate of 85 percent.

Comments

Most investigators who have tried this technique do not find it as reliable as the Doppler cerebrovascular examination and only a few major laboratories employ it. At the Martinez Veterans Administration Medical Center we found that this test had only approximately a 60 percent accuracy in 30 symptomatic patients with angiographically confirmed extracranial cerebrovascular disease. The commercial cost for two transducers, two amplifiers and one recorder is approximately $3,000.

Carotid Phonoangiography

Theory

Carotid stenosis produces turbulent flow which results in bruits.[10] The extent and amplitude of the bruits are analyzed with this technique.

Technique

The phonoangiogram transducers are placed over the base of the heart at the suprasternal notch and at least three places over the carotid, corresponding to the common carotid, the bifurcation and the internal carotid; recordings are made.

Experience

In one report utilizing an expensive computerized recording and playback system, Duncan and associates[11] found that if a stenosis was present which resulted in a residual lumen of approximately 0.5 to 2.5 mm, there was significant correlation in 88 of 98 cases of phonoangiograms with arteriography. The other cases were overestimated (seven) or underestimated (three).

Kartchner and McRae[12] reported on 208 patients (360 carotid arteries) who were examined using a commercial system (Narco Enterprises; cost approximately $3,000, Figure 2) and showed a diagnostic accuracy for this technique of 86 percent as determined by arteriography when the stenosis was over 40 percent. When compared with subsequent intraoperative flow measurements to determine hemodynamic significance, the accuracy was 72 percent (9 percent false positives and 19 percent false negatives). On a follow-up report concerning 1,287 asymptomatic patients with a neck bruit, 242 of these were found to have hemodynamically carotid bifurcation bruits.[13]

Figure 2.—Phonoangiography unit which displays bruits on oscilloscope screen and will produce photographs of same. (Courtesy of Narco Airshields Enterprises, Houston, Texas.)

Comments

Phonoangiography is largely used as an adjunct to oculoplethysmography. It will pick up a stenosis of 40 percent diameter or more but may be negative if the stenosis exceeds 95 percent to 98 percent. It does not detect nonstenotic ulcers, and requires a very quiet room for accuracy. When used alone its false negative rate is high.

We find that its usefulness is primarily in association with oculoplethysmography since it facilitates the detection of bilateral stenosis (oculoplethysmography can be normal under these

Figure 3.—Water transduction instrument, OPG-Kartchner, used for measurement of ocular pulsations that may reflect carotid stenosis. (Courtesy of Narco Airshields Enterprises, Houston, Texas.)

circumstances), external carotid stenoses which produce bruits and transmitted bruits. It can extend the accuracy of oculoplethysmography-Kartchner diagnosis from approximately 87 percent to 93 percent (50 patients).

Bruits may occur with stenoses as small as 35 percent; yet 75 percent stenosis is necessary for flow reduction. Its value in these circumstances is that it may provide earlier detection of small lesions and lead to appropriate follow-up. The sophisticated equipment giving best results may well cost $10,000 to $20,000, or more, and has never been used prospectively in a population survey.

Oculoplethysmography

Theory

The use of the oculoplethysmography (OPG) screening technique is second only to the Doppler periorbital examination in frequency of use. There are basically two types of instruments available: air transduction and water transduction. With earlier air instruments suction cups were placed on the sclera at high vacuum and caused considerable discomfort to the patient. Water (OPG-Kartchner) and newer air (Zira) instruments are more comfortable and simply rest on the cornea and are held there utilizing only small amounts of vacuum (Figure 3). Recent eye operations, ocular injury and retinal detachment are contraindications to the use of oculoplethysmography. The eye must be anesthetized and this may be contraindicated in some patients.

In the original OPG technique as developed by William Gee (air: zero to 300 mm of mercury vacuum), gradients of vacuum are applied to the eye as ocular pulsations are recorded through the same suction eye cup. Common carotid compression is carried out determining (by its effect on pulsation) the intraocular or internal carotid back pressure.

Water transduction and some air transduction instruments depend upon the timing of pulse intervals between the external and the internal carotid arteries; actual pressure may also be measured. Delays are believed to be due to carotid stenosis.

Experience

Gee reported 700 studies in 400 patients.[14] There were 67 cases with abnormal findings; of these, 6 were false positives. Two of the remainder had only ophthalmic artery occlusion.

McDonald[8] reported on 40 patients in whom 72 vessels had been examined with angiography. OPG by the Gee technique had an overall accuracy of 97 percent, with 3 percent false negatives, and 0 percent false positives. OPG by the Kartchner technique (water transduction) had a 74 percent overall accuracy with 24 percent false negatives and 3 percent false positives.

Gross reported an overall accuracy of 90 percent for the water transduction (Kartchner) and a 31 percent overall accuracy rate of air transduction (Gee) with 19 percent false positives and 50 percent false negatives for the air system.[15] He further reported that 50 percent in the latter group of patients had systolic pressures over 130 mm of mercury (the Gee system measures up to 110 mm of mercury intraocular pressure) and 33 percent of the latter group had bilateral lesions.

Comments

The debates between those advocating air and those advocating water transduction are quite vigorous as regards which technique is better. The largest experience is by Kartchner (water transduction) who has a 90 percent overall accuracy when the carotid stenosis is over 40 percent. A negative test does not always rule out bilateral disease or carotid bifurcation disease. It is often difficult to distinguish between stenosis and total occlusion.

Our experience with 100 patients examined with the OPG/CPA Kartchner machine confirms that the accuracy is roughly as reported (90 percent) when compared with angiography.

These systems cost approximately $10,000 and

Figure 4.—Continuous wave Doppler imaging unit used for imaging the extracerebral carotid artery system. Doppler probe is held over the neck and via a position sensing arm an image is projected on the oscilloscope screen. (Courtesy of Carolina Medical Electronics, King, North Carolina.)

have not as yet been used in a controlled prospective survey. While most of these units would appear to be reasonably efficient at detecting significant carotid stenosis their effect on stroke prevention is unknown. However, these systems are also less dependent on technicians in operation, reducing this variable. We use the OPG-Kartchner system and recommed it to those whose overhead can support the cost of this system.

Doppler Ultrasonic Imaging and Flow Velocity Analysis

Background

All of the aforementioned techniques will frequently not detect lesions narrowing the arterial lumen by less than 50 percent transverse diameter and, in addition, often do not distinguish bilateral abnormalities, multiple tandem lesions (extracranial versus intracranial), nor do they necessarily distinguish between significant stenosis versus total occlusion. Therefore, considerable effort has been directed toward developing a noninvasive technique which provides a picture similar to that of conventional angiography and which provides blood flow information at the same time. The currently available instruments are expensive (usually $25,000 or more) and for the most part still developmental.

Basically, there are two methods for imaging the carotid directly: continuous wave Doppler or pulsed Doppler. The best images are obtained at or near the bifurcation. All units can detect as little as a 25 percent decrease in arterial diameter but are not always consistent in performance.

Continuous Wave Doppler Ultrasonic Imaging

Theory and Technique

Developed by Reid and Spencer at the Institute of Applied Physiology and Medicine in Seattle, the continuous wave Doppler instrument is available from Carolina Medical Electronics as Dopscan. The Reid Doppler Continuous-Wave Flowmeter provides a directional analogue signal (A) which is proportional to the mean (W) of the Doppler-shifted audio signals and is also proportional to its amplitude squared; that is, $A = a^2w$. The imaging technique consists of placing the 5 MHz Doppler probe in a position sensing arm on a cam connected to an oscilloscope.[16] The technician then slides this back and forth over the carotid while listening to the audio signal which is tape recorded.

The expensive portion of the unit consists of instrumentation providing on an oscilloscope an image of the carotid which can be photographed (Figure 4). The absolute key to the unit, however, is the technician discerning the audio signal which discriminates between common, internal, external carotid arteries and the bifurcation. Various audible frequency shifts yield harmonics which to the trained ear mean normal, stenosis or calcification. The technician guides the probe according to these sounds and thus provides the image. The interpreter looks at the photograph of the image and listens to the tape for interpretation.

Experience

Spencer[17] reports 92 percent correlation with arteriography (8 percent false negative) in 54 patients with more than a 50 percent stenosis. Doppler supraorbital artery imaging examination, including ophthalmic artery flow readings, is done along with the imaging.

Comment

We are using this unit but have limited experience to date. It is definitely an improvement over the Doppler cerebrovascular examination but it costs approximately $25,000 (or more). The imaging is highly technician-dependent. This unit, with sophisticated frequency harmonic analysis,

Figure 5.—Example of a Doppler scanning instrument under development. This instrument attempts to combine extracerebral carotid flow and anatomic imaging information for a functional picture of the carotid artery. (Courtesy of SRI International, Inc., Menlo Park, California.)

could prove to be quite worthwhile and the potential for noninvasive studies associated with it is great.

Pulsed Doppler Carotid Imaging

Theory and Technique

This technique has been developed by Hokanson and is used by Barnes[18] as well as Strandness in Seattle.[19] A 5 MHz Doppler probe emits short bursts of ultrasound (approximately 1 microsecond) with a receiving crystal time-gated to receive at variable intervals following transmission. Similar to the Reid system, the probe is mounted in a position sensing arm which is connected to a display oscilloscope. Longitudinal cross section, transverse cross section and projectional views may be obtained with approximately six different areas viewed at once. Audio analysis of the sound can be done by direct interpretation, analogue output or sound spectral plot. It is possible to convert these signals to color-coded displays, but this is extremely expensive. At present this scanner sells for approximately $13,500.

Direct scanning of the carotid can be blocked by calcium in the wall of the vessel and provide what appears to represent a significant lesion. The interpretation of these shadows depends upon the sound spectrum analysis distal to these lesions.[18]

Results

Barnes[18] reports use of this system by itself and also with sound spectral analysis. He reports that vascular wall calcification interfering with ultrasound gave 20 false positive diagnoses in 36 normal internal carotid arteries. Combining sound spectral analysis with imaging permitted correct diagnosis in approximately 90 percent of 82 vessels studied and also identified 14 totally occluded arteries.

Comment

Although there are some excellent features, these techniques obviously require very expensive equipment and knowledgeable interpretation (audio analysis is necessary). These intruments are still developmental and need extensive trial before their costs can be justified. Nonetheless, the idea of combining velocity analysis and direct imaging holds considerable promise for the future.

Real-Time and High-Resolution Ultrasound Arteriography

Background and Theory

Basically, these techniques are being developed by Green, at SRI International in Menlo Park, California, and Mercier, at the Mayo Foundation in Minnesota.[20] SRI and Mayo Foundation have a joint effort to develop diagnostic methods and instrumentation for assessment of atherosclerotic disease. The latter is developing an instrument that contains a 10 MHz B-scan image that displays the carotid bifurcation in transverse and longitudinal cross section (Figure 5). A 5 MHz 20 point (gates) pulsed Doppler blood velocity profile is superimposed on the image. These two transducers are mounted in a scanning head that is gimballed and wall-mounted. This, in turn, feeds into a unit with two displays—one for direct viewing and one for photographic recording. Resolution of approximately 0.5 mm is achieved.

Experience

Many flaws have yet to be eliminated, but this would appear to be a promising instrument. The developmental instrument is intended to replace angiography and in experimental instances already has. The primary limitation of this technique is that the intracerebral circulation is not visualized.

Using the B-mode scanner alone on 21 vessels which had been angiogramed as well, Mercier found seven with a positive correlation, six with a close correlation, four false negatives and three

false positives.[20] The angiogram was felt to be false negative in another patient as well.

Occasional difficulty has been found with anatomic variations and in obese patients. In younger patients with less calcified plaques, the severity of the stenosis was usually underestimated. Ultrasound images often have a discontinuous and laminated appearance and, therefore, scanning by itself cannot differentiate between a minimal stenosis and total occlusion. The velocity profile will apparently do this.

Comment

This is a big step in the right direction; but many details have yet to be worked out and extensive clinical trial is necessary. The commercial scanners sold for vascular use have limits as described above and these still are quite serious limitations.

Velocity Wave Forms and Doppler Harmonic Analysis

Rutherford[21] using a directional Doppler probe ($850) and analogue recorder (approximately $2,000) has reported using velocity wave form analysis in the diagnosis of extracranial cerebrovascular disease. Several statisticians were required and they developed a discriminant equation using peak systolic velocity, end disastolic velocity, peak diastolic velocity, width-to-height ratio of systolic velocity, and peak and diastolic velocity slope. Recordings were made over the common carotid arteries in 20 patients and 18 younger, presumed normal subjects. In addition 15 patients were examined with less than 50 percent stenosis, 13 with over 50 percent stenosis and 9 with complete occlusion. The accuracy rate in separating normal, stenosed and occluded arteries was 100 percent. The accuracy of discriminating between stenosis greater or less than 50 percent was 82 percent. In addition, it was reported that in 21 of 37 of these patients who had occlusive disease there were normal supraorbital artery Doppler examination results.

Comment

This technique is mentioned to illustrate the potential for further development of Doppler recording of carotid artery flow—a pathway that appears to hold great promise. This analysis using already developed equipment appears to be more sensitive than other currently employed and available methods.

As has been mentioned earlier, the Doppler shifts and the harmonics they display—when listened to by an experienced examiner—can often reveal sounds characteristic of flow proximal or distal to stenoses and occlusions, and around even small plaques. Using a real time sound spectrum analyzer[22,23] it is possible to display frequency patterns that predict the location and significance of stenoses.

Discussion

It is unfortunate that many expensive instruments have been placed on the market before their true value in such areas as screening for a stroke-prone population has been assessed. Much of the data obtained by more expensive units can be obtained in a somewhat different manner by less costly, commercially available units. All of these noninvasive cerebrovascular tests have yet to be adequately evaluated in regard to the screening and detection of lesions that may or may not be of clinical significance to the patient in his lifetime. Other lesions such as atherosclerotic plaques which may ulcerate and lead to stroke may be overlooked. The dynamics of the intracranial circulation are not assessed by most of these methods either. Only time and carefully controlled studies will permit the determination of their true value. As both medical and surgical modalities now exist that are efficacious for stroke prevention, it is hoped that continued development of instrumentation will produce survey techniques to aid in this important goal.

At present we feel that, despite its limitations, the Doppler cerebrovascular examination is the best of the available tests based on cost alone. For thousands of dollars more one can get somewhat improved results in patients with stenotic lesions, but we do not think the greater expense is practical. If one is willing to spend more, then one of the oculoplethysmographs is recommended because their results are as good as or better than those of any other noninvasive test and less dependent on technicians.

Future developments will undoubtedly produce reliable and reproducible scanning techniques that give visual anatomic images as well as blood velocity information. One of the benefits of this would be differentiation of extracranial carotid

disease from intracranial carotid disease, a process that is not done well using current techniques.

REFERENCES

1. Bone GE, Barnes RW: Limitations of the Doppler cerebrovascular examination in hemispheric cerebral ischemia. Surgery 79:577-580, May 1976

2. Russell HE, Burger RJ, Barnes RW: The Doppler ultrasonic cerebrovascular examination: Improved accuracy by refinement of technique. Twentieth Annual Conference, American Institute of Ultrasound in Medicine, Oct 1975, Winston-Salem, NC

3. Barnes RW, Russell HE, Bone GE, et al: Doppler cerebrovascular examination: Improved results with refinements in techniques. Stroke 8:468-471, Jul-Aug 1977

4. Lye CR, Sumner DS, Strandness DE: The accuracy of the supraorbital Doppler examination in the diagnosis of hemodynamically significant carotid occlusive disease. Surgery 79:42-45, Jan 1976

5. Brockenbrough EC: Screening for the prevention of stroke: Use of a Doppler flow meter. Information and Education Resource Support Unit, Seattle, Washington/Alaska Regional Medical Program, 1969

6. Wise G, Brockenbrough EC, Marty R: The detection of carotid artery obstruction: A correlation with arteriography. Stroke 2:105-113, Mar-Apr 1971

7. Moore WS, Bean B, Burton R, et al: The use of ophthalmosonometry in the diagnosis of carotid artery stenosis. Surgery 82:107-115, Jul 1977

8. McDonald PT, Rich NM, Collins GJ, et al: Comparison of Doppler cerebrovascular examination, oculoplethysmography and ocular pneumoplethysmography for detection of carotid disease: A prospective clinical study. International Cardiovascular Society 26th Meeting, Los Angeles, 1978. Arch Surg 113:1341-1349, Nov 1978

9. Barnes RW, Garrett WV, Slaymaker EE, et al: Doppler ultrasound and supraorbital photoplethysmography for noninvasive screening of carotid occlusive disease. Am J Surg 134:183-186, Aug 1977

10. Gurll N, Dewey CF, Lees RS: Phonoangiography: A noninvasive technique for diagnosis of arterial disease. Circulation 44(Suppl 2):173, 1971

11. Duncan GW, Gruber JO, Dewey CF, et al: Evaluation of carotid stenosis by phonoangiography. N Engl J Med 293:1124-1128, Nov 27, 1975

12. Kartchner MM, McRae LP, Mirrison FD: Noninvasive detection and evaluation of carotid occlusive disease. Arch Surg 106:528-535, 1973

13. Kartchner MM, McRae LP: Noninvasive evaluation and management of the asymptomatic carotid bruit. Surgery 82:840-847, Dec 1977

14. Gee W, Oller DW, Wylie EJ: Noninvasive diagnosis of carotid occlusion by ocular pneumoplethysmography. Stroke 7:18-21, Jan-Feb 1976

15. Gross WS, Verta MJ, VanBellen B, et al: Comparison of noninvasive diagnostic techniques in carotid artery occlusive disease. Surgery 82:271-278, Aug 1977

16. Spencer MP, Reid JM, Davis DL, et al: Cervical carotid imaging with a continuous wave Doppler flowmeter. Stroke 5:145-154, Mar-Apr 1974

17. White D, Brown RE (Eds): Ultrasound in Medicine, Vol 3B. New York, Plenum Publishing Corporation, 1977, p 129

18. Barnes RW, Bone GE, Reinertson J, et al: Noninvasive ultrasonic carotid angiography: Prospective validation by contrast arteriography. Surgery 80:328-335, Sep 1976

19. Mozersky DJ, Hokanson DE, Summer DS, et al: Ultrasonic visualization of the arterial lumen. Surgery 72:253-259, Aug 1972

20. Bernstein EF (Ed): Noninvasive Diagnostic Techniques in Vascular Disease, St Louis, CV Mosby Co, 1978, pp 29-39

21. Rutherford RB, Hiatt WR, Kreutzer E: The use of velocity wave form analysis in the diagnosis of carotid artery occlusive disease. Surgery 82:695-702, Nov 1977

22. Giddens DP, Mabon PF, Cassanove RA: Measurements of disordered flows distal to subtotal vascular stenoses in the thoracic aorta of dogs. Circulation Res 39:112-119, Jul 1976

23. Reinertson JE, Barnes RW: Carotid flow velocity scattering: Diagnostic value in Doppler ultrasonic arteriography. Clin Res 24:594A, 1976

When Patients Are Choking

INSTRUMENTATION for foreign body removal has changed somewhat. . . . Misapplication of the Jackson cannulated foreign body forceps or misunderstanding as to their proper handling has resulted in some preference for the use of center action forceps, although it has a less delicate tactile field. . . . Our Foreign Body Committee has interdicted the hasty application of emergency methods of foreign body removal if the patient is moving air. Dr. Heimlich pointed out "I think for the first time—that the choking patient is silent . . . [not] coughing or wheezing."

—GABRIEL F. TUCKER, JR, MD, *Chicago*

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Adriamycin (Doxorubicin) Cardiotoxicity: A Review

ROWAN T. CHLEBOWSKI, MD, PhD, *Torrance, California*

Adriamycin (doxorubicin hydrochloride) is an antineoplastic agent effective against a wide range of malignant conditions, although cardiac toxicity, especially dose-dependent cardiomyopathy, limits its long-term use. Previous mediastinal radiation therapy or left ventricular dysfunction and advanced age increase the risk of this complication developing. Unfortunately, there is no readily available, noninvasive method that can predict Adriamycin-induced congestive heart failure (CHF). However, both endomyocardial biopsy and radionuclide ejection-fraction measurement are promising techniques which may soon permit selection of patients who can safely receive this drug. At present, Adriamycin-induced CHF can best be prevented by limiting the total dose as follows: 400 to 450 mg per sq meter following mediastinal radiation and 500 to 550 mg per sq meter for patients without other significant risk factors. Consideration of dose-response data and use of a weekly schedule may soon permit the administration of Adriamycin for long-term antineoplasm therapy.

ADRIAMYCIN (doxorubicin hydrochloride), an antitumor antibiotic, has been established as an effective agent against a wide range of malignant conditions.[1,2] Unfortunately, the long-term use of this drug is limited by cardiac toxicity, especially drug-induced congestive heart failure (CHF).[3-5] Adriamycin cardiac toxicity includes a broad clinical spectrum, and both early and late effects are described.[6]

Early effects are those which can be observed after one dose of anthracycline and include a pericarditis-myocarditis syndrome, acute left ventricular dysfunction and arrhythmias. The pericarditis-myocarditis syndrome has rarely been observed after administration of high doses of daunomycin, but it carries a poor prognosis and can occur in patients in whom there was no cardiac disease before treatment.[7] Pericarditis-myocarditis following administration of Adriamycin has not been reported, probably because high doses of this drug have been used less frequently than high doses of daunomycin. Left ventricular dysfunction resulting in acute congestive heart failure, another early effect of anthracycline administration, appears mainly in patients who had borderline cardiac compensation before treatment, and may be secondary to the transient left ven-

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tricular dysfunction that occurs one to two days following the use of Adriamycin.[8] Arrhythmias, both atrial and ventricular, occur in up to 26 percent of patients receiving Adriamycin.[9,10] The clinical significance of these arrhythmias is unclear; however, cases of *sudden death* have been reported during therapy with this drug.[10] At present, coronary artery disease is not a contraindication to its use.

A late effect of the administration of Adriamycin in some patients has been a dose-related cardiomyopathy which may progress to overt congestive heart failure.[3,4] Factors influencing this drug-induced CHF are the focus of this review.

Adriamycin-induced CHF often occurs only after a latent period following administration of the last dose of the drug. The median length of this period has exceeded two months in several series.[11,12] Therefore, determination of the expected incidence of this complication is difficult, because some patients with progressive malignancy die during the latent period while others may no longer be under close observation when this complication occurs. The best estimate for the overall incidence of drug-induced CHF in patients receiving Adriamycin is 2.2 percent.[11] The risk of developing cardiomyopathy increases with cumulative doses of the drug as follows: rare for those receiving less than 500 mg per sq meter; approximately 10 percent for those receiving between 550 and 600 mg per sq meter, and about 30 percent for patients receiving more than 600 mg per sq meter.[13,14] The relationship between cumulative dosage and CHF has led investigators to suggest that the total dose of Adriamycin should not exceed 500 to 550 mg per sq meter in any patient.[2,3] Adriamycin-induced CHF was initially felt to be unresponsive to therapy, with mortality resulting in approximately 50 percent of the patients discussed in most early series.[4,12] However, earlier diagnosis and initiation of treatment with digitalis, diuretics and so forth can result in substantial clinical improvement in most patients.[15]

Risk Factors

Although there is considerable variation from person to person in cardiac tolerance to Adriamycin, several groups of patient are at higher risk for developing drug-induced cardiomyopathy. Patients who have received previous mediastinal radiation therapy (especially those who received the equivalent of 600 rads to the apex of the heart) are more sensitive to Adriamycin,[16] as are patients older than 70 years.[17] There is a 20-fold increase in the incidence of Adriamycin-induced CHF among patients with both of these predisposing factors.[17] Most large series do not support the theory that previous therapy with cyclophosphamide is a significant risk factor for the development of cardiac toxicity.[11,17] This result is somewhat surprising because cyclophosphamide given in high doses has been associated with cardiac dysfunction.[18] Relatively few patients with a preexisting cardiac disease that has limited left ventricular function have received Adriamycin because many protocols excluded such persons. However, as even relatively low doses of the drug can reduce left ventricular function,[8] patients with reduced cardiac reserve are poor candidates for Adriamycin therapy.

Pathologic lesions associated with Adriamycin-induced CHF in humans have been studied in both autopsy and right ventricular endomyocardial biopsy specimens. These biopsy studies, done in association with a cardiac catheterization procedure, were developed in conjunction with the heart transplant program at Stanford. Using this technique, two principal types of myocyte injury have been described: myofibrillar loss and vacuolar degeneration of the myocytes. Both types of change can occur with preservation of normal mitochondrial architecture, and only after apparent myocyte death does mitochondrial degeneration occur. The severity of the pathologic involvement, as seen on electron microscopy, can be graded on a scale from 0 (normal) to 3 (diffuse cellular involvement). Using this system, myocardial changes were noted in essentially all patients receiving more than 240 mg per sq meter of Adriamycin.[19,20,31] In addition, the degree of morphologic change induced by the drug was dose related. Therefore, the endomyocardial biopsy technique provides a useful method for monitoring Adriamycin-induced CHF in a research setting to facilitate identification of risk factors and to permit assessment of other, less invasive techniques.

The specific pathophysiologic mechanism of Adriamycin-induced cardiomyopathy that underlies the morphologic changes seen on electron microscopy is unknown; however, a variety of mechanisms have been proposed. Myers and coworkers[21] suggested that the muscle lesions are,

in part, the result of unrestrained free radical reactions which lead to peroxidation of the membrane components. The following factors support this proposal: the potential of anthracyclines to generate free radicals, and the amelioration of Adriamycin cardiac toxicity in the mouse by concomitant administration of alpha-tocopherol (vitamin E)[21,22] and acetyl cysteine,[23] both antagonists of free radical formation. The role of these agents in preventing cardiac damage in patients receiving Adriamycin is under investigation at several centers. Inhibition of the coenzyme Q10 (CoQ10) in cardiac tissue by doxorubicin has also been suggested as a possible mechanism for anthracycline-induced cardiac damage. CoQ10 is found in mitochondria and is required for coupling respiration to oxidative phosphorylation.[24] Although only limited evidence supports this theory at present, administration of CoQ10 has reduced Adriamycin cardiac toxicity in rabbits.[25] Such results suggest that agents which antagonize the deleterious effects of this drug on cardiac muscle may permit safer clinical use of Adriamycin in the future. In this regard, the investigational chemotherapeutic agent ICRF-159 prevented myocardial toxicity of Adriamycin in a perfused canine heart system[26] while drug-induced CHF was not observed during a large clinical trial of an Adriamycin and ICRF-159 combination.[27] At present, however, no antagonist of this drug-induced CHF has passed sufficient clinical trial to warrant routine use.

Predicting Drug-Induced Ventricular Dysfunctions

Research has focused on identifying noninvasive measurements that would permit detection of drug-induced ventricular dysfunction before clinical signs and symptoms develop. A correlation has been described between Adriamycin-induced congestive heart failure and a fall in the sum of the QRS voltage in electrocardiographic limb leads. In one series, a voltage decrease of more than 30 percent was seen in 16 of 17 patients in whom heart failure occurred, and in only 8 of 36 patients treated with similar Adriamycin dosages, but in whom congestive heart failure did not develop.[28] It should be noted that the presence of pronounced pleural effusion complicates use of this technique.[29] Similarly, the systolic time interval, determined by echocardiographic assessment, has been reported to be valuable in facilitating detection of Adriamycin-induced cardiomyopathy.[15] Unfortunately, neither QRS voltage decrease nor determination of systolic time interval correlates with left ventricular performance at cardiac catheterization or with endomyocardial pathologic biopsy score.[20] In addition, it has been noted that even a normal systolic time interval just before administration of the drug does not preclude the occurrence of CHF as a result of that dose.[30] Recently, the usefulness of electrocardiographic voltage changes and changes in systolic time intervals were evaluated prospectively at the Sidney Farber Cancer Institute.[8] In patients with neoplastic disease and a life expectancy of more than a year, serial electrocardiograms and systolic time interval determinations were done. If the published criteria[13] for stopping administration of Adriamycin were followed, 23 of the 103 patients would have received less than 450 mg per sq meter. However, all patients continued to receive Adriamycin until a full dose of greater than 400 mg per sq meter was given; no drug-induced CHF was observed in any patient after a median follow-up of ten months. The authors concluded that "clinical examinations and dose limitations of about 500 mg per sq meter are still the simplest, least expensive, and most reliable guide to the proper use of the anthracyclines."[8]

At present, therefore, no readily available, noninvasive methodology exists that permits reliable monitoring of cardiac function in patients receiving Adriamycin. Use of the invasive endomyocardial biopsy technique may allow identification of patients who can safely continue to receive Adriamycin beyond currently established total dose levels.[17,31] In addition, the new technique of radionuclide angiography may soon prove to be a sensitive and reliable means of noninvasive cardiac monitoring. This method uses technetium-labeled red blood cells and a gamma scintillation camera to determine left ventricular ejection fraction. In one series of 30 patients, the ejection fraction determined by this technique correlated with ejection fractions measured by cardiac catheterization.[32] Radionuclide angiography was also used in a recent study of 55 patients receiving Adriamycin.[33] In that report, left ventricular ejection fraction measured by radionuclide angiography could be correlated with the cumulative doses of Adriamycin received. In addition, the ejection fraction declined to less than 30 percent of the pretreatment value in all

five patients in whom clinical CHF occurred. However, other patients in the study who were at risk for CHF had a short follow-up interval of only one to four months. Therefore, before the routine use of this expensive radionuclide scanning technique can be recommended for all patients receiving Adriamycin, other studies involving longer follow-up need to be done to confirm its value in predicting CHF.

Some experimental data suggest that larger total doses of Adriamycin may be given if the schedule for administration is changed. In 1976 Weiss and co-workers[34] reported the results of the Central Oncology Group's (COG) experience with administering Adriamycin to patients in weekly injections of 0.4 mg per kg of body weight. In this study of 442 patients, 50 patients received more than 600 mg per sq meter and no definite cases of cardiac toxicity were reported. This was a startling result because previous experience using a dosage schedule of every three weeks had shown that patients receiving more than 600 mg of Adriamycin per sq meter were at about 30 percent greater risk for the occurrence of drug-induced CHF.[13,14] Similarly, Chlebowski and colleagues[35] reported no drug-induced CHF in 336 patients treated by the Western Cancer Study Group (WCSG) with weekly doses of Adriamycin. A retrospective analysis by Von Hoff and associates[11] (which included the COG and WCSG data) of over 4,000 patients who received Adriamycin on various treatment schedules confirmed the lower incidence of cardiac toxicity among patients using the weekly schedule. Preliminary data on giving Adriamycin to patients by a continuous infusion schedule over 10 to 48 hours have suggested that use of this schedule also may limit cardiac damage.[36,37]

Both the weekly[38] and the continuous infusion schedules[37] are associated with greatly decreased peak plasma levels of Adriamycin. A physiologic pharmacokinetic model has been developed to predict Adriamycin concentrations found in tumors and healthy organs for the various schedules of administration. Using this model, a theoretical advantage to the use of schedules that decrease the peak level of Adriamycin has been proposed,[39] based on decreased exposure of heart tissue to the threshold level of Adriamycin required for myocyte injury.[40] Because clinical experience with weekly administration of the drug is limited compared with its use every three weeks, the clinical effectiveness of the weekly schedule has not been established. However, both of these schedules of Adriamycin administration are undergoing randomized trials at several institutions to assess their relative clinical effectiveness.

Another approach that may permit long-term use of Adriamycin is determining the lowest dose which will be effective in treating each type of tumor. Some data on dose-response curves for Adriamycin have suggested effective dosages lower than the "standard" dosage for selected tumor groups.[41] For example, randomized trials for determining appropriate dosage levels for treating breast cancer have established that dosages of 20 mg per sq meter given on days 1 and 8 and then every 28 days thereafter may be equivalent to regimens involving higher dosage levels of 60 mg per sq meter given every 21 days.[42] Therefore, consideration of dose-response characteristics and changes in administration schedules may permit longer-term use of Adriamycin, with less risk of cardiac toxicity. Finally, anthracycline analogs that present less risk of causing cardiac toxicity than the parent Adriamycin are under investigation.[43]

Conclusions

At present, Adriamycin-induced CHF can best be prevented by limiting the total dose of the drug. For patients with previous cardiac radiation therapy, a limited dose of 400 mg per sq meter is suggested. For patients without other significant risk factors, such as advanced age (more than 70 years old) or previous left ventricular dysfunction, a limited dose of 500 to 550 mg per sq meter is suggested.

There is, as yet, no available method which assures the safe administration of Adriamycin after a total dosage has been given. However, both endomyocardial biopsy and radionuclide ejection fraction are promising techniques which may soon provide ways to predict those who can safely continue to receive the drug.

Administration of Adriamycin on a weekly schedule is associated with fewer cases of drug-induced CHF; however, the antineoplastic effectiveness of this dosage schedule has yet to be established. In treating selected tumors, consideration of dose-response data may permit giving the drug in lower doses, thereby extending the time of its use. Finally, the administration of antagonists to Adriamycin's deleterious effects

on the myocardium may permit safer use of this drug in the future.

REFERENCES

1. Wang JJ, Cortes E, Sinks LF, et al: Therapeutic effect and toxicity of Adriamycin in patients with neoplastic disease. Cancer 28:837-843, 1971

2. Blum RH, Carter SK: Adriamycin: A new anticancer drug with significant clinical activity. Ann Intern Med 80:249-259, 1974

3. Gottlieb JA, Lefrak EA, O'Bryan R, et al: Fatal Adriamycin cadiomyopathy: Prevention by dose limitation. Proc Am Assoc Cancer Res and ASO 14:88, 1973

4. Lefrak EA, Pitha J, Rosenheim S, et al: A clinico-pathologic analysis of Adriamycin cardiotoxicity. Cancer 32:302-314, 1973

5. Benjamin RS: A practical approach to Adriamycin toxicity. Cancer Chemother Rep 3:191-194, 1975

6. Bristow MR, Billingham ME, Mason, JW, et al: Clinicial spectrum of anthracycline antibiotic cardiotoxicity. Can Treat Rep 62:873-879, 1978

7. Bristow MR, Thompson PO, Martin RP, et al: Early anthracycline cardiotoxicity. Am J Med 65:823-832, 1978

8. Henderson IC, Sloss LJ, Jaffe N, et al: Serial studies of cardiac function in patients receiving Adriamycin. Cancer Treat Rep 62:923-929, 1978

9. Cortes EP, Lutman G, Wanka J, et al: Adriamycin cardiotoxicity: A clinico-pathologic correlation. Cancer Chemother Rep 6:215-225, 1975

10. O'Bryan R, Luce J, Talley R, et al: Phase II evaluation of Adriamycin in human neoplasia. Cancer 32:1-8, 1973

11. Von Hoff DD, Layard M, Basa P, et al: Analysis of risk factors for development of Adriamycin-induced congestive heart failure. Proc Am Asso Can Res and ASCO 19:215, 1978

12. Rinehart JJ, Lewis RP, Balcerzak SP: Adriamycin cardiotoxicity in man. Ann Intern Med 18:475-478, 1974

13. Minow RA, Benjamin RS, Gottlieb JA: Adriamycin cardiomyopathy—An overview with determination of risk factors. Cancer Chemother Rep 6:195-201, 1975

14. Lefrak EA, Pitha J, Roseheim S, et al: Adriamycin cardiomyopathy. Cancer Chemother Rep 6:203-208, 1975

15. Balcerzak SP, Christakis J, Lewis RP, et al: Systolic time intervals in monitoring Adriamycin-induced cardiotoxicity. Cancer Treat Rep 62:893-899, 1978

16. Billingham ME, Bristow MR, Glatstein E, et al: Adriamycin cardiotoxicity: Endomyocardial biopsy evidence of enhancement by irradiation. Am J Surg Pathol 1:17-23, 1977

17. Bristow MR, Mason JW, Billingham ME, et al: Adriamycin cardiomyopathy: Evaluation by phonocardiography, endomyocardial biopsy and cardiac catheterization. Ann Intern Med 88:168-173, 1978

18. O'Connell TX, Besenbaum MD: Cardiac and pulmonary effects of high doses of cyclophosphamide and isophosphamide. Cancer Res 34:1586-1591, 1974

19. Billingham ME, Mason JW, Bristow MR, et al: Anthracycline cardiomyopathy monitored by morphologic changes. Cancer Treat Rep 62:865-875, 1978

20. Mason JW, Bristow MR, Billingham ME, et al: Invasive and noninvasive methods of assessing Adriamycin cardiotoxic effects in man: Superiority of histiopathologic assessment using endomyocardial biopsy. Cancer Treat Rep 62:857-864, 1978

21. Myers CE, McGuire W, Young R: Adriamycin: Amelioration of toxicity by tocopherol. Cancer Treat Rep 60:961-962, 1976

22. Kimball JC, Lantin E, Wang YM: Vitamin E and N-acetyl-L-cysteine modification of Adriamycin toxicities. Proc Am Assoc Can Res and ASCO 20:188, 1979

23. Doroshow JH, Locker GY, Myers CE: Prevention of doxorubicin cardiac toxicity by N-acetyl-L-cysteine. Proc Am Assoc Can Res and ASCO 20:253, 1979

24. Folkers K: Survey on the vitamin aspects of coenzyme Q. Int Z Vitaminforsch 39:334-352, 1969

25. Bertazzoli C, Sala L, Solcia E, et al: Experimental Adriamycin cardiotoxicity prevented by ubiquinone in vivo in rabbits. Int Res Commun Sys Med Sci 3:468, 1975

26. Herman EH, Mhatre RM, Lee JP: Prevention of the cardiotoxic effects of Adriamycin and daunomycin in the isolated dog heart. Proc Soc Exp Biol Med 140:234-239, 1972

27. Chlebowski RT, Pugh R, McCracken J, et al: A phase I-II trial of combination therapy with Adriamycin and ICRF. Proc Am Assoc Can Res and ASOC 20:199, 1979

28. Minow RA, Benjamin RS, Lee ET, et al: QRS voltage change with Adriamycin administration. Cancer Treat Rep 62: 931-934, 1978

29. Ali MK, Soto PA, Maroongwge E, et al: Electrocardiographic changes after Adriamycin chemotherapy. Cancer 43:465-471, 1979

30. Minow RA, Gottlieb JA, Frazin L, et al: Adriamyin cardiotoxicty (Letter). Ann Intn Med 82:855-857, 1975

31. Benjamin RS, Ewer MS, MacKay B, et al: An endomyocardial biopsy study of anthracycline-induced cardiomyopathy: Detection, reversibility and potential amelioration. Proc Am Assoc Can Res and ASCO 20:372, 1979

32. Kennedy JW, Scrensen SG, Ritchie JL, et al: Radionuclide angiography for the evaluation of anthracycline therapy. Cancer Treat Rep 62:941-943, 1978

33. Alexander J, Dainiak N, Berger HJ, et al: Serial assessment of doxorubicin cardictoxicity with quantitative radionuclide angiocardiography. N Engl J Med 300:278-283, 1979

34. Weiss AJ, Metter GE, Fletcher WS, et al: Studies on Adriamycin using a weekly regimen demonstrating its clinical effectiveness and lack of cardiac toxicity. Cancer Treat Rep 60: 813-822, 1976

35. Chlebowski RT, Pugh R, Paroly W, et al: Adriamycin on a weekly schedule: Clinically effective with low incidence of cardiotoxicity. Clin Res 27:53A, 1979

36. Legha SS, Benjamin RS, Yap MY, et al: Augmentation of Adriamycin's therapeutic index by prolonged continuous I.V. infusion for advanced breast cancer. Proc Am Assoc Can Res and ASCO 20:261, 1979

37. Gercovich FG, Praga C, Boretta G, et al: Ten-hour continuous infusion of Adriamycin. Proc Am Assoc Can Res and ASCO 20:372, 1979

38. Chan KK, Cohen JL, Gross JF, et al: Prediction of Adriamycin disposition in cancer patients using a physiologic, pharmacokinetic model. Cancer Treat Rep 62:1161-1171, 1978

39. Chen HG, Gross JF, Chlebowski RT, et al: The use of physiological pharmacokinetics to predict cardiotoxicity of Adriamycin regimens. Submitted to Cancer Treat Rep 1979

40. Haskell CM, Sullivan A: Comparative survival in tissue culture of normal and neoplastic human cells exposed to Adriamycin. Cancer Res 34:2991-2994, 1974

41. O'Bryan RM, Baker LH, Gottlieb JR, et al: Dose response evaluation of Adriamycin in human neoplasia. Cancer 39:1940-1948, 1977

42. Creech RH, Catalano RB, Harris DT, et al: Low versus high dose Adriamycin therapy of metastatic breast cancer. Proc Am Assoc Can Res and ASCO 19:315, 1978

43. Henderson IC, Billingham M, Israel M, et al: Comparative cardiotoxicity studies with Adriamycin (ADR) and Ad32 in rabbits. Proc Am Assoc Can Res and ASCO 19:158, 1978

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The Epidemiology of Thyroid Cancer in Los Angeles County

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More than 300 new cases of thyroid cancer are diagnosed in Los Angeles County every year. The age-adjusted annual incidence rates of this disease for all races combined are 2.4 for males and 6.1 for females. Rates for women are more than twice rates for men in each major ethnic group. Blacks of both sexes have the lowest rates; Japanese, Chinese, other Asians and Spanish-surnamed whites all have rates that are as high as or higher than rates among non-Spanish-surnamed whites. Other demographic patterns include the excess of thyroid cancer among Jewish residents of Los Angeles.

There have been an increase in thyroid cancer incidence and a decline in mortality for this disease in the United States over the past several decades. Several possible explanations can be made for these trends. Also, the risk factors for thyroid cancer deserve review.

LOS ANGELES is a convenient place to study the patterns of occurrence of a relatively rare type of cancer such as thyroid cancer. Although thyroid cancer accounts for only 1.4 percent of all new malignant lesions diagnosed among Los Angeles residents, the Cancer Surveillance Program (CSP)[1] collects reports on the more than 300 new cases diagnosed each year among the 7 million county residents. We will present information, derived from CSP reports, describing the pattern of thyroid cancer occurrence in Los Angeles and will compare this pattern with those in other areas.

Average age-adjusted annual incidence rates for all races combined for 1972 to 1976 in Los Angeles were 6.06 in females and 2.41 in males (H. R. Menck, unpublished data, 1978), with an overall female-to-male sex ratio of 2.5:1. Los Angeles rates are similar to those reported from other areas in the United States, whose rates, like those reported for Cali, Colombia, and for Israel, are among the highest in the world.[2]

Figure 1, which shows Los Angeles incidence rates by race and sex, illustrates that for each major ethnic group female rates are two to seven times higher than male rates. Los Angeles blacks have the lowest rates; this finding agrees with reports of low rates for blacks in other areas of the United States.[2] The rates among men and women with Spanish surnames were not significantly different from rates among other whites. The total number of cases of thyroid cancer among Asians was too small for differences to be significant, but annual age-adjusted incidence rates were uniformly higher among Asian women than among

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whites without Spanish surnames: Chinese women had a rate of 7.44 and Japanese women a rate of 7.51. A total of 27 cases occurred among other nonwhite women, predominantly Filipino, Korean, Thai, Vietnamese and Samoan—an annual rate of 13.00. Chinese and Filipino women in Hawaii also had high rates—higher than those for Hawaiian whites or Hawaiian Japanese.[2]

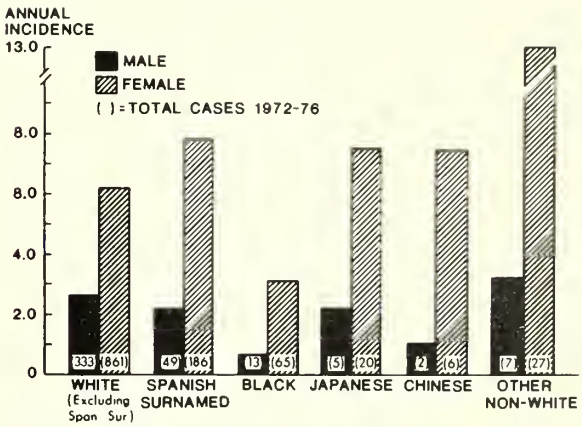

Figure 1.—Distribution of thyroid cancer cases by race, Los Angeles County, 1972 to 1976.

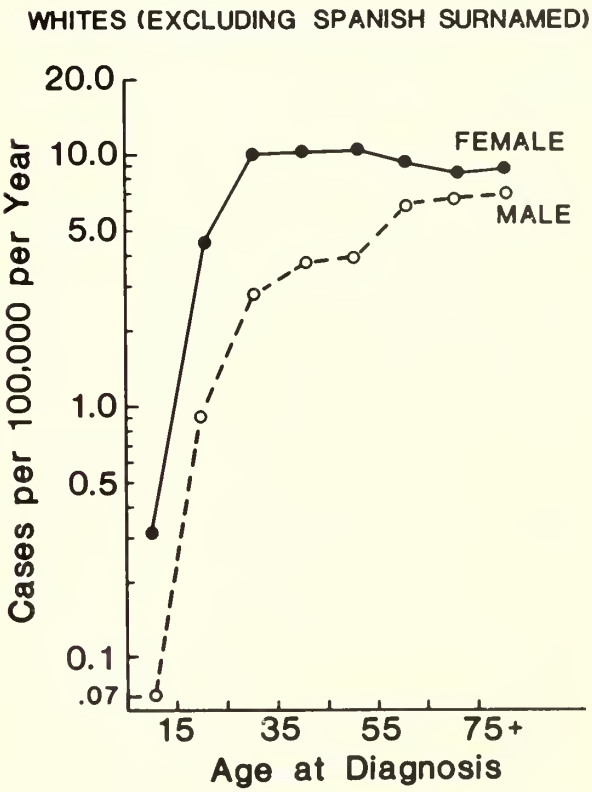

Figure 2.—Thyroid cancer: Average age-specific annual incidence rates, Los Angeles County, 1972 to 1976.

Incidence by Age and Sex

Figure 2 shows the age curves of thyroid cancer incidence for white men and women in Los Angeles, and Figure 3 shows the female-to-male sex ratio for each age group. For the youngest age group (0 to 14 years) the female rate was more than four times the male rate. Incidence among females increased rapidly, remained high during reproductive years and declined somewhat after menopause. Incidence among males, in contrast, increased more steadily throughout life, with male rates approaching female rates in the oldest age groups.

Table 1 shows the distribution of incidence by social class for males and females and the female-to-male sex ratio for each class. The sex ratio was similar for all classes. In addition, we see no trend relating social class to incidence.

Analysis of CSP occupational data on white males (excluding those with Spanish-surnames), who were 20 to 64 years old in 1972 to 1974 when their tumors were diagnosed, shows that

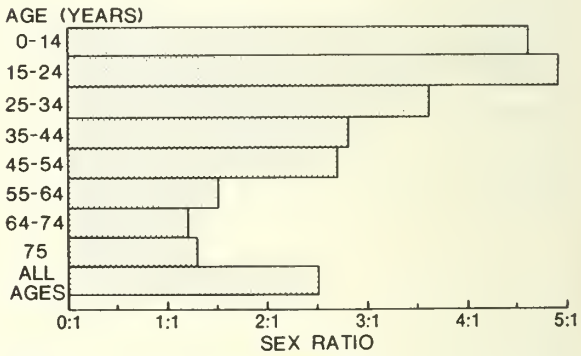

Figure 3.—Sex ratio of female to male incidence for whites (excuding Spanish surnamed) for thyroid cancer, Los Angeles County, 1972 to 1976.

TABLE 1.—*Frequency and Annual Age-Adjusted Incidence Rates of Thyroid Cancer by Sex and Social Class* for Whites (Excluding Spanish-Surnamed), Los Angeles County, 1972 to 1976*

Social Class	*Males*		*Females*		*Female:Male Sex Ratio*
	Number	*Rate*	*Number*	*Rate*	
1 (High) ...	44	3.90	99	7.07	1.8:1
2	98	2.92	245	6.35	2.2:1
3	85	2.65	243	6.41	2.4:1
4	82	2.02	232	5.01	2.5:1
5 (Low) ...	22	3.02	42	7.14	2.4:1
Unknown ..	2	...	0	...	...
TOTAL ...	333	2.65	861	6.07	2.3:1

*Each case was assigned the social class of the census tract he resided in at the time of his thyroid cancer diagnosis. Census social class is determined by use of a weighted sum of average family income and average educational level of people over age 23.

a greater than expected number of thyroid cancer cases occurred among workers in certain occupations. These included physicians (4 observed, 0.8 expected), engineers (4 observed, 0.8 expected), salesmen (14 observed, 5.0 expected) and managers (17 observed, 9.6 expected). The number of cases in any one occupational group, however, was too small for any firm conclusions to be drawn.

When we compared the distribution of religious affiliations of all thyroid cancer patients to those of all cancer patients in Los Angeles, we observed that a greater than expected number of thyroid cancer patients were Jewish. This was true for both males and females. From 1972 to 1976, a total of 75 of our male cases were Jewish (2.5 times the number expected), and 170 of our female cases were Jewish (twice the number expected). This finding agrees with a report from Israel of higher rates for Jews than for non-Jews.[2]

Figure 4 illustrates the distribution of thyroid cancer cases in Los Angeles by histologic type for each sex. The distributions were similar for men and women, with papillary carcinoma the most common. Other types (in order by frequency) are mixed papillary and follicular carcinoma, follicular carcinoma, medullary carcinoma and other types that include carcinoma or adenocarcinoma (not otherwise specified), giant cell carcinoma, small cell carcinoma, Hurthle cell carcinoma, reticular cell sarcoma, squamous cell carcinoma, mucinous carcinoma, serous pap cyst, perithelial sarcoma and unspecified lymphoma.

Trends in Thyroid Cancer Occurrence

In our studies we saw no trends in thyroid cancer occurrence over the course of five years, but trends are evident from other national surveys. Age-adjusted thyroid cancer mortality has decreased for whites (both male and female), but has not changed significantly for nonwhites. Thyroid cancer accounts for only 0.5 percent of all female and 0.2 percent of all male deaths from cancer.[3] Unlike mortality, incidence of thyroid cancer has increased by a factor of three over the last four decades.[4] How much of this difference is real is uncertain; part of it may be attributable to an increase in diagnostic efficiency. The fact that this increase has occurred only in people younger than 50 suggests that some of the increase may be attributable to radiation-induced tumors.[4] Because radiation treatment of benign conditions of infancy and childhood was not common until the late 1920's, such exposure was limited to those born in the last 50 or 60 years.

Risk Factors for Thyroid Cancer

Four major categories of risk factors for thyroid cancer have been discussed in some detail in a recent review paper[5]: genetics, thyroid dis-

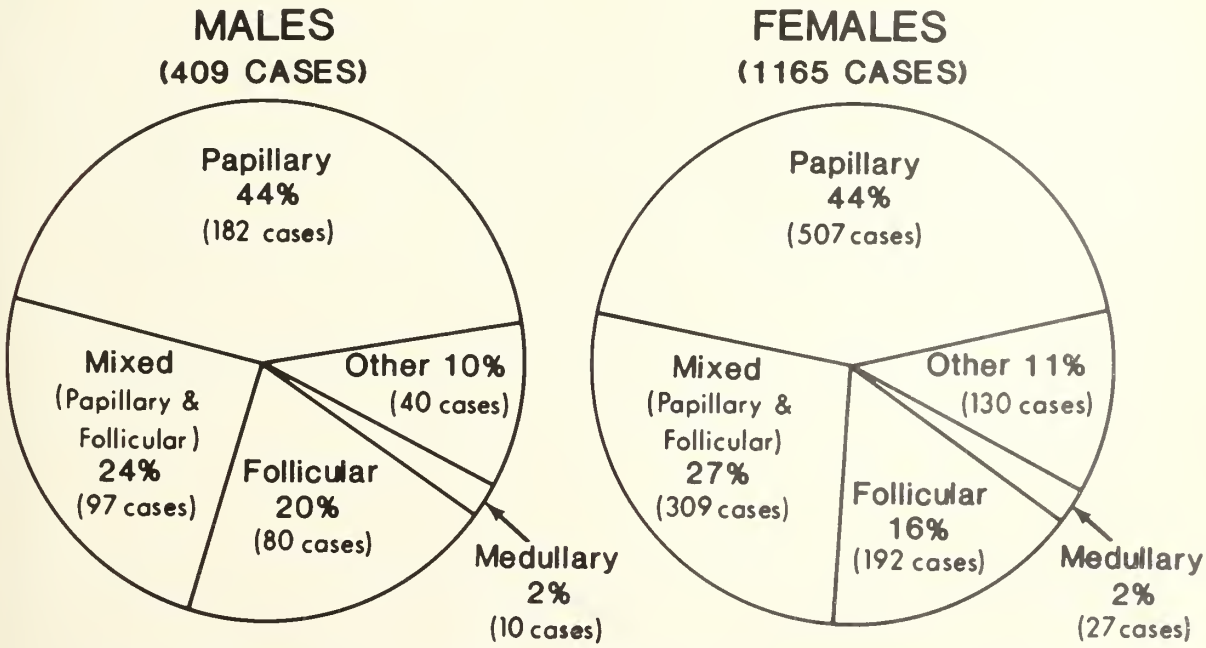

Figure 4.—Distribution of thyroid cancer by histologic type, Los Angeles County, 1972 to 1976.

ease, iodine deficiency and radiation. Some cases of thyroid cancer do occur in association with recognized familial syndromes, but such cases account for only a small proportion of the total. Other cases of thyroid cancer have occurred in persons with Graves disease or Hashimoto thyroiditis, but the issue of whether these immunogenetic disorders are specific precursors for thyroid carcinoma remains unresolved. Some geographic areas known for endemic goiter had high thyroid cancer rates which declined after iodine was added to residents' diets. This relationship between goiter and thyroid cancer is not consistent around the world, however.[6]

By far the best substantiated of all thyroid cancer risk factors is a history of exposure to ionizing radiation. Radiation-exposed cohorts known to have high rates of thyroid cancer include people who received head or neck radiation treatment for benign childhood conditions, A-bomb survivors and Marshall islanders exposed to radioactive fallout.[7,9] Continued observation of persons who received iodine 131 treatment as children or adolescents for thyrotoxicosis may show an increased risk in this group as well.[10] Various host factors at the time of exposure enhance this high risk; these include young age at exposure, high levels of thyroid stimulating hormone at exposure and gender (female).[11] There is a greater incidence of thyroid cancer as doses of radiation increase, but an increment in incidence is evident for even relatively low doses.[12]

REFERENCES

1. Hisserich JD, Martin SP, Henderson BE: An areawide cancer reporting network. Public Health Rep 90:15-17, 1975
2. Waterhouse J, Muir C, Correa P, et al: Cancer Incidence in Five Continents—Vol 3. Lyon, France, International Agency for Research on Cancer, 1976
3. Cancer statistics, 1976. CA 26:14-29, 1976
4. Cancer in Connecticut: Incidence and Mortality Rates 1935-1974. Hartford, Connecticut Tumor Registry, (In Press)
5. Schottenfeld D, Gershman ST: Epidemiology of thyroid cancer—Part III. Clin Bul 7:98-104, 1977
6. Ramalingaswami V: Iodine and thyroid cancer in man, *In* Hedinger CE (Ed): Thyroid Cancer. Berlin, Springer-Verlag, 1969, pp 111-123
7. Favus MJ, Schneider AV, Stachura ME, et al: Thyroid cancer occurring as a late consequence of head and neck irradiation. N Engl J Med 294:1019-1025, 1976
8. Parker LN, Belsky JL, Yamamoto T, et al: Thyroid carcinoma after exposure to atomic radiation. Ann Intern Med 80: 600-604, 1974
9. Conrad RA: A twenty-year review of medical findings in a Marshallese population accidentally exposed to radioactive fallout. Upton, New York, Brookhaven National Laboratory, 1973
10. Hayek A, Chapman EM, Crawford JD: Long-term results of treatment of thyrotoxicosis in children and adolescents with radioactive iodine. N Engl J Med 283:949-953, Oct 29, 1970
11. Hempleman LH, Hall WJ, Phillips M, et al: Neoplasms in persons treated with X-rays in infancy: Fourth survey in 20 years. J Natl Cancer Inst 55:519-530, 1975
12. Modan B, Ron E, Werner A: Thyroid cancer following scalp irradiation. Radiology 123:741-744, 1977

Retrolental Fibroplasia

IN CONTRAST to the decades of the 40's and 50's, who gets retrolental fibroplasia today? . . . He's the sickest baby in the nursery. He's the one who needs the most in the way of life support systems, just to keep him alive. Respiratory distress syndrome and multiple spells of apnea are two respiratory diseases, if you will, that seem to predispose to retrolental fibroplasia.

—JOHN T. FLYNN, MD, *Miami, Florida*

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The Clinical Physiology of Water Metabolism

Part I: The Physiologic Regulation of Arginine Vasopressin Secretion and Thirst

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Water balance is tightly regulated within a tolerance of less than 1 percent by a physiologic control system located in the hypothalamus. Body water homeostasis is achieved by balancing renal and nonrenal water losses with appropriate water intake. The major stimulus to thirst is increased osmolality of body fluids as perceived by osmoreceptors in the anteroventral hypothalamus. Hypovolemia also has an important effect on thirst which is mediated by arterial baroreceptors and by the renin-angiotensin system. Renal water loss is determined by the circulating level of the antidiuretic hormone, arginine vasopressin (AVP). AVP is synthesized in specialized neurosecretory cells located in the supraoptic and paraventricular nuclei in the hypothalamus and is transported in neurosecretory granules down elongated axons to the posterior pituitary. Depolarization of the neurosecretory neurons results in the exocytosis of the granules and the release of AVP and its carrier protein (neurophysin) into the circulation. AVP is secreted in response to a wide variety of stimuli. Change in body fluid osmolality is the most potent factor affecting AVP secretion, but hypovolemia, the renin-angiotensin system, hypoxia, hypercapnia, hyperthermia and pain also have important effects. Many drugs have been shown to stimulate the release of AVP as well. Small changes in plasma AVP concentration of from 0.5 to 4 μU per ml have major effects on urine osmolality and renal water handling.

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General Concepts of Water Metabolism

IN NORMAL HUMANS, osmolality, or the concentration of osmotically active solutes in body fluids, is remarkably constant despite large variations in water and solute intake and excretion. Every kilogram of body water contains 285 to 290 mOsm of solute, consisting primarily of salts of sodium in extracellular fluid and of potassium in intracellular fluid. The identical osmolality of intracellular and extracellular fluids is produced by free movement of water across all cellular and subcellular membranes, governed only by the physical forces of osmosis and diffusion. A gain or loss of free water will be shared by all major body compartments (vascular, interstitial and intracellular) in proportion to their relative sizes. The single exception to this free movement is the control of water permeability of the distal portion of the mammalian nephron by arginine vasopressin (AVP), antidiuretic hormone. Among all vertebrates, only mammals (and to some extent, birds) possess the unique ability to excrete a hyperosmotic urine and thus conserve free water when the supply of available water is limited. It has been suggested that this ability of the mammalian kidney to concentrate fluids may have played an important role in our ultimate domination over the dinosaurs and other reptiles at the end of the Mesozoic era. There is a continuous decrease in the proportion of total body water (and particularly the extracellular compartment) with growth and aging, as well as a difference between men and women (Table 1).

The day-to-day fluctuations in total body water in a normal person are very small, amounting to approximately 0.2 percent of body weight per 24 hours. Although infants have a relative *excess* of body water and extracellular volume as related to total body weight, the surface area, oxygen consumption, cardiac output, insensible water loss, renal water excretion and overall metabolism are all high in relation to total body water. Therefore, when one compares these fundamental metabolic measurements with total body water, infants and young children are seen to be more vulnerable to water deficit and dehydration than adults.[1]

The average normal intake and loss of water in a day by an adult human is given in Table 2. Even with maximal renal conservation of water, the body is unable to prevent a continuous loss of insensible fluid through the skin, lungs and gastrointestinal tract. For the replacement of this extrarenal loss, a person must rely on adequate water ingestion. Humans and other mammals vary considerably in their need for an exogenous source of water in their diet during maximal renal conservation. Of all mammals, only certain desert rodents can minimize their renal and extrarenal water losses sufficiently to maintain their water balance from that available in the preformed and oxidative water found in the desert plants they ingest. These rodents can concentrate their urine to a level four to five times greater than that of humans, and by living in underground burrows

ABBREVIATIONS USED IN TEXT

AVP = arginine vasopressin
CSF = cerebrospinal fluid
U/P = urinary to plasma (ratio)

TABLE 1.—*Body Water Compartments Throughout Life Span**

Age	*Sex*	*Body Weight (Kg)*	*Extracellular Water (Percent)*	*Intracellular Water (Percent)*	*Total Body Water (Percent)*
0-11 days ...			41.6	34.8	76.4
11-180 days ..			34.9	37.9	72.8
½-2 years ...			27.5	34.7	62.2
2-7 years ...			25.6	36.9	62.5
7-14 years ..			17.5	46.7	64.2
23-54 years ..	♂	72.5	23.4 ± 0.64	30.9 ± 0.89	54.3 ± 1.39†
23-51 years ..	♀	59.3	22.7 ± 0.54	25.9 ± 0.96	48.6 ± 1.47
71-84 years ..	♂	68.1	25.4 ± 1.36	25.4 ± 0.58	50.8 ± 1.55
61-74 years ..	♀	63.9	21.4 ± 0.45	22.4 ± 0.97	43.4 ± 1.32

*Modified from Parker HV, Olesen KH, McMurrey J, et al: *In* Ciba Foundation, Colloquia on Ageing, Vol 4. Boston, Little, Brown and Company, 1958.

†Standard error of the mean.

TABLE 2.—*Average Daily Intake and Output of Water in a Normal Adult Human**

Water Intake (ml)			*Water Output (ml)*		
Source	*Obligatory*	*Facultative*	*Source*	*Obligatory*	*Facultative*
Drink	650	1,000	Urine	700	1,000
Preformed .	750	....	Skin	500	....
Oxidative ..	350	....	Lungs	400	....
			Feces	150	....
Subtotals .	1,750	1,000	Subtotals .	1,750	1,000
Total	2,750	....	Total	2,750	....

*From Wolf AV: Thirst. Springfield, IL, Charles C Thomas, 1958.

they reduce to a minimum their insensible pulmonary and cutaneous water loss.[2] Humans, in contrast, even when forming maximally concentrated urine, require some exogenous source of free water to replace continued insensible and minimal renal losses of water.

The day-to-day regulation of body water is dependent, therefore, on the kidneys and on a receptor system for signaling the relative need for water ingestion. This signal, thirst, plays an essential role in the regulation of the volume and tonicity of the body fluids. The sensation of thirst is dependent on excitation of the cortical centers of consciousness. Although the sensation of thirst may be modified somewhat by stimuli arising in the oropharynx or gastrointestinal tract, it is doubtful that in humans these local stimuli are of great importance.[3]

Hypothalamic Thirst Centers

Although thirst is a cortical or conscious sensation, it has been clearly established that there exist in the hypothalamus specific nuclear centers essential for the integration of various types of signals altering water ingestion.[3-5] The local instillation of hypertonic solutions of chloride or direct electrical stimulation of this area in goats leads to profound polydipsia culminating in severe water intoxication, with an increase in body weight of as much as 40 percent. Destruction of these same centers causes pronounced hypodipsia or complete adipsia. These animals then develop profound hypertonic dehydration, but show no distinct inclination to drink. Stimulating and inhibitory impulses are transmitted from these centers to the cerebral cortex and consciousness, thereby transforming the need, or lack of need, for water into appropriate behavior. Furthermore, impulses of cortical or voluntary origin can readily condition the sensation of thirst and create what might be called the thirst *appetite,* or voluntary habits of drinking. These vary greatly from individual to individual, psychogenic polydipsia representing the extreme form of excessive ingestion. Conversely, in humans, injury to these centers, or the failure of hypothalamocortical impulses to stimulate thirst in a stuporous or unconscious patient, will cause inadequate water ingestion despite need.

The thirst centers lie in close proximity to the hypothalamic nuclei which regulate the production and release of antidiuretic hormone or arginine vasopressin. In view of this proximity, it is surprising that pathologic processes do not produce simultaneous disturbances in thirst regulation and AVP release more frequently. Physiologically, these centers must be carefully integrated in the maintenance of normal total body water. It is not surprising, therefore, that the major stimuli for thirst also cause the release of AVP and the renal conservation of water—the *water repletion reaction.* Those stimuli which in-

TABLE 3.—*Known Stimuli and Inhibitors of Thirst and the Release of Arginine Vasopressin*

Stimuli

Osmotic

Contracted intracellular volume of osmoreceptor neurons due to hyperosmolality of extracellular fluids (water loss or infusions of hypertonic solutions of molecules that do not freely permeate the blood-brain barrier, such as sodium chloride or mannitol)

Nonosmotic

- Decreased arterial pressure (? pulse pressure) in carotid and, possibly, aortic baroreceptors, resulting from vascular or extracellular volume contraction or fall in cardiac output
- Decrease in tension in the left atrial wall and great pulmonary veins because of reduced intrathoracic blood volume (such as blood loss, quiet standing, upright position and positive-pressure breathing)
- Pain
- Psychosis
- Increased temperature of blood perfusing the hypothalamus
- Drugs (acetylcholine and other cholinergic drugs, morphine, barbiturates, nicotine, adrenergic agents), ? chlorpropamide, clofibrate, carbamazepine, cyclophosphamide, vincristine
- Carotid body chemoreceptor stimulation by hypoxia or hypercapnia
- Stimulation of the renin-angiotensin system

Inhibitors

Osmotic

Expansion of intracellular volume of the neurons of supraoptic hypophyseal nuclei secondary to hyposmolality of extracellular fluids (water ingestion)

Nonosmotic

- Increased arterial pressure (? pulse pressure) in carotid and, possibly, aortic baroreceptors secondary to vascular or extracellular volume expansion, with rise in cardiac output
- Increase in tension in left atrial wall and great pulmonary veins secondary to increased intrathoracic blood volume (such as hypervolemia, reclining position, negative-pressure breathing, immersion in water up to neck, acute cold exposure with peripheral vasoconstriction and shift of blood centrally)
- Occasionally, emotional stress
- Decreased temperature of blood perfusing the hypothalamus
- Drugs (alcohol, diphenylhydantoin, ? norepinephrine, narcotic antagonists [oxilorphan, butorphanol], ? anticholinergic drugs)
- ? inhibition of the renin-angiotensin system

hibit thirst also inhibit the release of AVP and therefore initiate water diuresis—the *water depletion reaction.*[6]

Thirst Stimuli and Inhibitors

The major physiologic stimulus for thirst is a decrease in total body water, with or without cellular dehydration (Table 3). The usual sensation of thirst, and its subcortical stimulus, in a normal person is the result of a 1 percent to 2 percent contraction of total body water with a comparable rise in the osmolality of body fluids and slight cellular dehydration. In more severe cases of water depletion, or water loss in excess of sodium, substantial cellular dehydration and hyperosmolality of all body fluids will occur. Cellular dehydration with pronounced thirst will also occur, even with an increased total body water, if hypertonic solutions of sodium chloride, glucose, mannitol and so forth, are given to the point of producing hyperosmolality of the body fluids. Of equal importance, the decrease in total body water may result from a primary iso-osmotic contraction of the extracellular phase, such as hemorrhage, vomiting, diarrhea, massive saline diuresis, or a rapid accumulation of ascites or intraluminal gastrointestinal fluid *(third space).*

Under these circumstances, thirst may be induced even in the face of hyponatremia and cellular overhydration and, in fact, may even aggravate the latter. Stricker has shown that cellular overhydration in association with, or at the expense of, extracellular volume will frequently produce severe thirst in rats.[6,7] This hypovolemic thirst is permanently satisfied only when the extracellular or intravascular volume is repleted. Clinically, thirst may occur despite massive expansion of total body water or of interstitial fluid volume and despite hyponatremia, when *effective* (nonsplanchnic) circulating blood volume, blood pressure and cardiac output are reduced, such as in severe congestive heart failure, cirrhosis of the liver (during the rapid accumulation of ascites or edema) and the nephrotic syndrome. Whenever a patient complains of thirst despite adequate ingestion of water, or when a deficit of water per se does not seem to exist, one should immediately consider the possibility of a diminished vascular or extracellular volume, or reduced cardiac output and blood pressure, or both.

Such *inappropriate* stimulation of thirst in patients with normal osmolality or hyposmolality may also occur with normal or elevated blood pressure. In these situations there is overactivity of the renin-angiotensin system which in turn stimulates thirst. For example, intense thirst has been noted in patients with malignant hypertension or in hypertensive patients overtreated with diuretic therapy.

The exact mechanism(s) by which a reduction in vascular and extracellular volume stimulates the hypothalamic thirst centers is unknown. Although it is probable that pure water depletion with its accompanying hyperosmolality of body fluids and contraction of intracellular volume would affect the receptor cells of the hypothalamus directly, it is not obvious that iso-osmolar or hyposmolar contraction of the extracellular volume would do the same. However, because it is clear the latter can cause the release of AVP by stimulation of intrathoracic and carotid sinus baroreceptors (Table 3),[8-13] these same receptors may well represent the receptors initiating the reflex arc responsible for nonosmolar stimulation of thirst. Recently, excellent studies have strongly implicated the renin-angiotensin system in the control of hypovolemic (hypotensive) thirst[14-21] and in the release of antidiuretic hormone.[18,22-29] The drinking produced by iso-osmotic depletion of intravascular volume,[14] by hypotension accompanying beta-adrenergic activation with isoproterenol and by constriction of the aorta above the renal arteries[19] is abolished by nephrectomy but survives sham nephrectomy and ureteral ligation.[14,19] In hypotensive rats, in which the kidneys have been removed, renin administered systemically and angiotensin II given intracranially (anterior hypothalamus) caused the animals to begin drinking again.[14,15,17,20] It, therefore, seems likely that low cardiac output, hypovolemia or hypotension, by stimulating the release of renin from the kidneys and the formation of angiotensin II, may cause thirst by a direct effect of the angiotensin II on the thirst regulatory centers in the hypothalamus. It is clear that any physiologic or pathologic change that causes a renal release of renin and the generation of angiotensin will stimulate or contribute to the stimulation of thirst and the release of antidiuretic hormone as well.

The exact neurotransmitters responsible for the activation of the hypothalamic component of thirst regulation are not known. However, several experiments in animals have shown that local hypothalamic application of cholinergic and adrenergic agents as well as heat and cold can profoundly influence both their relative drives for

food and water and their fluid excretion.[30-33] Recently, local administration of prostaglandin E (PGE) has also been found to stimulate both thirst and AVP release.[34] Furthermore, PGE augments the action of either angiotensin or hypertonic saline on central release of AVP.[35,36] These data suggest a possible central role for PGE in the modulation of thirst and AVP release.

Warming of the hypothalamus leads to a decrease in food intake, an increase in water intake and a decrease in urinary output, the water repletion reaction. Cooling of the hypothalamus leads to the reverse reactions. Similarly, rats, during dehydration, automatically decrease their ad libitum food intake to maintain proper integration of total body water and solute. Cholinergic agents (carbachol) applied directly to the hypothalamus stimulate the water repletion reaction and inhibit food intake. These reactions can be blocked by anticholinergic drugs, whereas the application of the alpha-adrenergic, norepinephrine, stimulates food intake, inhibits water intake and enhances urinary volume, the water depletion reaction. In addition, systemic administration of norepinephrine directly inhibits the action of AVP on the nephron. In contrast to norepinephrine, beta-adrenergic agents such as isoproterenol hydrochloride (Isuprel), when applied locally, stimulate the classic water repletion reaction, which can be completely inhibited by the simultaneous application of the beta-adrenergic blocking drugs. Finally, Fitzsimons and Setler[37] have clearly shown that interference with catecholaminergic systems in the diencephalon (preoptic region) by local instillation of catecholamine antagonists substantially inhibited angiotensin-induced drinking, but had little effect on cholinergic-induced drinking. The latter was completely inhibited by atropine. These findings suggest that the final common pathway for the central effect of angiotensin on the thirst mechanism involves stimulation of the adrenergic (beta) neurotransmitters of this area of the hypothalamus.

These experimental observations should be considered when the eating, drinking or urinary flow patterns of a given patient seem to be altered while the patient is receiving cholinergic or adrenergic drugs or their inhibitors, or in clinical situations in which the renin-angiotensin II system is stimulated.

Various organic hypothalamic lesions may alter thirst to the extent that adipsia, severe hypertonic dehydration and sustained hypernatremia may occur.[37,38,40] These lesions may be traumatic or inflammatory (such as encephalitis), or may involve eosinophilic granuloma, histiocytosis, internal hydrocephalus, craniopharyngioma, pinealoma and, in rare cases, so-called essential hypernatremia with a defect in thirst regulation in which no specific lesion may be found. In some patients diabetes insipidus or anterior pituitary insufficiency, or both, may also be present.

Polydipsia and polyuria are common symptoms in patients with chronic hypercalcemia or hypokalemic syndromes. Although a pronounced defect in the ability of the kidneys to concentrate urine may contribute to the polyuria, we have noted that polydipsia may be present despite the patient's ability to form a moderately hypertonic urine (400 to 700 mOsm per liter), and that the polydipsia may disappear after correction of hypercalcemia and hypokalemia long before any basic improvement in the concentrating abnormality has occurred. These observations suggest that the electrolyte disorder may cause a primary disturbance in thirst regulation. Recently, Berl and co-workers[39] have confirmed this clinical observation by noting that in potassium-depleted rats a primary polydipsia was responsible for the polyuria rather than the concentrating defect. Because potassium depletion now has been shown to be a strong stimulus to enhanced PGE synthesis, it is possible that this polydipsia is PGE induced. As calcium ion is a specific biologic antagonist of potassium, it would not be surprising to find that hypercalcemia also stimulates PGE synthesis.

Arginine Vasopressin, Antidiuretic Hormone

Arginine vasopressin (AVP) acts on the renal tubule and, in doing so, has a fundamental role in the homeostatic regulation of the volume and osmolality of the body fluids in mammals. The integration of AVP release with the thirst mechanism is necessary to assure the maintenance of a normal water content and osmolality in the body fluids. It is readily apparent that a distortion in the thirst mechanism without a corrective response in the renal handling of water, or a primary disorder in the renal handling of water without an appropriate corrective response in the thirst mechanism, will result in a serious distortion of the volume and osmolality of body fluids.

The Neurohypophyseal System

In mammals the neurohypophyseal system responsible for the synthesis, storage and release of

AVP consists of a group of specialized hypothalamic nuclei (supraoptic and paraventricular) and the neurohypophyseal tract, made up of the axons originating from these nuclei and terminating in the pars nervosa or posterior lobe of the pituitary.

A discrete neural lobe with its systemic blood supply first appears phylogenetically in Amphibia (Figure 1). These semiterrestrial vertebrates required a carefully regulated system for the retention and elimination of water; the neural lobe supplied the hormone (arginine vasotocin) for this purpose. The neural lobe in the earlier vertebrates appeared to be a structure totally surrounded by the anterior pituitary (Figure 1), and the peptides formed in this area probably served primarily as releasing factors for anterior pituitary hormones.

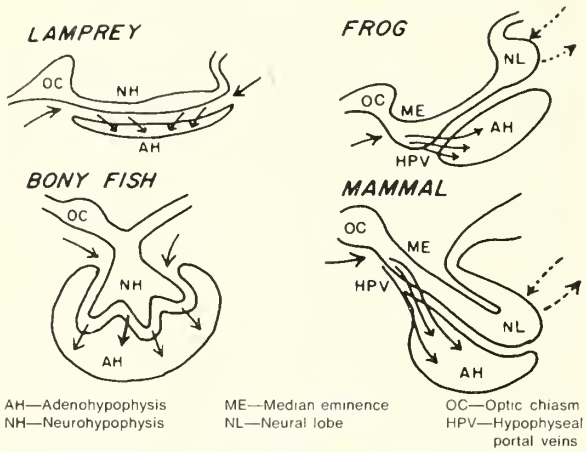


Figure 1.—Highly schematic diagrams of the hypophyseal circulation in four vertebrate types. Solid arrows represent blood flow from neurohypophysis to adenohypophysis. Broken arrows represent the blood flow to and from the neural lobe. (From Sawyer WH, et al: Circulation, 1960, Suppl, part 2, 21:1028. Reproduced with permission of the author and The American Heart Association.)

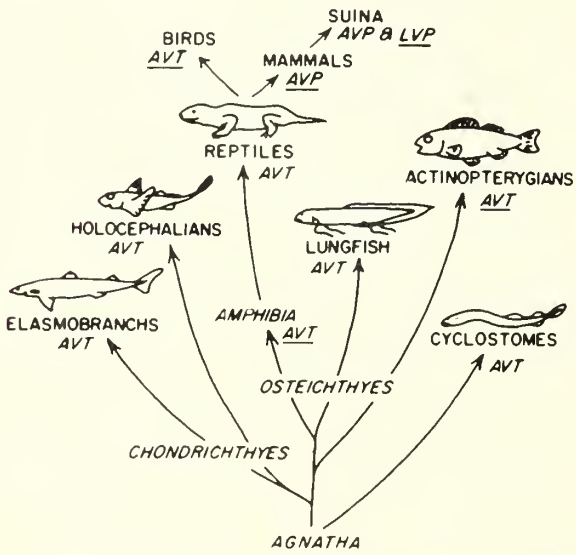


Figure 2.—The distribution of antidiuretic-vasopressor neurohypophyseal principles among the various major groups of vertebrates. AVP = arginine vasopressin; LVP = lysine vasopressin; AVT = arginine vasotocin. Underlining of the abbreviation indicates that the peptide has been chemically identified in at least one member of the phyletic group. (Reproduced with permission from Sawyer.[42])

Neurohypophyseal Peptides

However, despite the absence of a distinct neural lobe, biologically active octapeptides have been identified in the neurohypophyseal extracts of lower vertebrates; these are listed in Table 4.[41] Only three of these principles were considered by Sawyer and others to be antidiuretic hormones: arginine vasopressin, lysine vasopressin and arginine vasotocin. All three contain a basic amino acid in the penultimate position of the side chain, a molecular configuration responsible for their strong antidiuretic and vasopressor properties. The remaining natural peptides resemble oxytocin more closely in that they contain a neutral amino acid in the 8-position of the side chain. These have relatively weak vasopressor and antidiuretic effects. The exact chemical structure of arginine vasopressin and lysine vasopressin was determined by du Vigneaud and his associates after they defined the structure of oxytocin. As in the case of oxytocin, they confirmed the exactness of the chemical configuration by synthesizing peptides with biologic properties identical to those of the natural principles that they had isolated from beef and hog posterior pituitaries.

Arginine vasopressin appears to be present in representative species from most of the major groups of mammals, including the egg-laying monotremes and the marsupials. Lysine vasopressin has been found only in pituitaries from members of the division Suina (suborder Suiformes), which contains pigs, peccaries and hippopotami. All members of the other suborder of Artiodactyla that have been examined, the ruminants, appear to secrete arginine vasopressin. Although lysine vasopressin occurs in all three living families of the Suina, it has not entirely replaced arginine vasopressin. One of five pituitaries from the wild boar contained arginine vasopressin as well as lysine vasopressin. This species is believed to be ancestral to the domestic pig, suggesting that the

TABLE 4.—*The Known Active Neurohypophyseal Hormones of Vertebrates**

Peptide	Positions of Amino Acids† 3	4	8	Where Found
Antidiuretic vasopressor (basic) principles:				
Arginine vasopressin	Phe	Gln	Arg	Most mammals
Lysine vasopressin	Phe	Gln	Lys	Suina
Arginine vasotocin	Ile	Gln	Arg	All (?) vertebrates
Oxytocin-like ("neutral") principles:				
Oxytocin	Ile	Gln	Leu	Mammals, ratfish
Mesotocin	Ile	Gln	Ile	Nonmammalian tetrapods, lungfishes
Isotocin	Ile	Ser	Ile	Ray-finned fishes
Glumitocin	Ile	Ser	Gln	Rays
Valitocin	Ile	Gln	Val	Spiny dogfish (? other sharks)
Aspartocin	Ile	Asn	Leu	Spiny dogfish (? other sharks)

*From Sawyer WH: Am Zool 17:728, 1977.
†Common structure: Cys-Tyr--3--4--Asn-Cys-Pro--8--Gly(NH_2)

ability to synthesize arginine vasopressin may have been lost by domestic pigs as an indirect result of selective breeding. Because the synthesis of vasopressin is almost certainly genetically determined, this implies that the gene allowing lysine-vasopressin synthesis originated by mutation, occurring in a species ancestral to the Suina. Figure 2[41] shows the distribution of antidiuretic-vasopressor neurohypophyseal hormones among the various groups of vertebrates. In general, the bony fishes as well as the teleosts have only one neurohypophyseal hormone, vasotocin. Some teleosts and holocephalians contain a second active principle called isotocin (Table 4). This peptide may also be present in lungfish. The elasmobranchs may have two different neutral peptides: arginine vasotocin and glumitocin (Table 4).

Vasotocin, having the ring of oxytocin and side chain of vasopressin, produces both antidiuretic and milk-ejection effects when injected into mammals, but it is not nearly as potent in this regard as vasopressin. Vasotocin enhances water transport in the nephrons of birds, reptiles and amphibians but not in bony fishes, cartilaginous fishes or cyclostomes; it appears to enhance sodium excretion in these latter vertebrates (Table 5).[41] Extraordinarily low doses of vasotocin (10^{-16}M) have been shown to have potent effects on the contraction of the oviduct of the mud puppy (Necturus maculosus) during the spring.[42] This action of vasotocin reflects its oxytocic as opposed to its vasopressor properties.

Vasotocin has also been identified in the posterior pituitary of fetal mammals as well as in the pineal glands and subcommissural organs of adult mammals.[43-45] Its function in mammals is not known although it has been shown to have potent antigonadotrophic and prolactin-releasing effects after intravenous or intracerebroventricular injection.[46,47]

TABLE 5.—*Responses to Synthetic Arginine Vasotocin Described as Occurring in Representatives of the Major Phyletic Groups of Vertebrates**

Group	Urine Flow	Filtration Rate	Sodium Excretion	Permeability to Water: Skin	Permeability to Water: Bladder
Mammals	−	0	0, +		
Birds	−	0			
Reptiles	−	−	−	..	0
Amphibians	−, 0	0, −	0, −	+, 0	+, 0
Lungfishes	+	+	+	0	
Teleosts	+	+	+	0	
Cyclostomes	0	..	+	0	

+ = increase; − = decrease; 0 = no change. Where two signs appear species differ in their responses to arginine vasotocin.

*From Sawyer WH.[42]

Osmoreceptors for AVP Release

For sometime it was believed that the magnocellular neurons in the hypothalamus were capable of sensing changes in plasma osmolality, thereby releasing vasopressin. There is now evidence that there are multiple osmosensitive areas outside the supraoptic and paraventricular nuclei. Using the technique of microinjection of hypertonic solutions into various locations in the central nervous system, Peck and Blass[48] identified separate osmoreceptors mediating thirst and vasopressin release. The osmoreceptor centers were scattered within the preoptic areas and anterior hypothalamus. The electrophysiologic studies of Hayward and colleagues have suggested that there are different functional types of osmosensitive cells (specific and nonspecific) and that these

cells are one synapse removed from the neurosecretory neurons. Van Gemert and co-workers[49] have shown that lesions made in the medial preoptic area, with the supraoptic nuclei spared, resulted in polyuria and impaired vasopressin release. These observations have pointed to regulatory centers for thirst and AVP release outside the neurosecretory nuclei.

Formation and Storage of AVP

The posterior lobe of the pituitary is the storage site for the AVP and oxytocin formed in the nerve cell bodies in the supraoptic and paraventricular nuclei. Although the content of oxytocin and AVP in the posterior pituitary are approximately equal, and frequently both hormones are released together, selective release appears to occur when certain physiologic stimuli are applied; for example, hemorrhage causes AVP release, whereas distention of the cervix and suckling cause the release of oxytocin. In autopsy material we have found the AVP content of the posterior pituitary in humans to be 85 ± 15 units per mg relative to the *United States Pharmacopeia* International Standard, and others have reported approximately 15 USP units per whole human gland.

Electron microscopic and other histologic studies of the neurohypophyseal system strongly suggest that the membrane-bound neurosecretory granules that are formed by the nerve cell bodies of the supraoptic nuclei are carried by axoplasmic streaming down the axons which terminate as bulbous expansions on the basement membranes of the capillaries in the posterior lobe. The granules containing the peptide hormones and their carrier proteins gradually enlarge as they descend along their intra-axonal path to their storage site in the posterior lobe.

Rosenfeld,[50] in 1940, and van Dyke and colleagues,[51] in 1942, isolated a protein from the posterior lobe of the ox pituitary gland. Bioassay showed constant oxytocic pressor and antidiuretic activities. This material, often called the van Dyke protein, was thought to contain the biologically active principles of the posterior lobe. In the mid-1950's, Acher and associates[52,53] noted the relationship between the peptide hormones oxytocin and vasopressin and the cystine-rich van Dyke protein (extracted from bovine pituitaries). They found that oxytocin and vasopressin could be reversibly separated from the larger binding proteins, and they suggested the name neurophysin for the hormone-free proteins. The findings of Acher and his associates were confirmed by Ginsburg and Ireland.[54] The latter investigators, as well as Dean and Hope,[55] found that the neurophysins were stored in the same subcellular organelles (neurosecretory granules) as oxytocin and vasopressin, and they have come to be regarded as the physiologic *carrier proteins* for the intraneuronal transport of the hormones from their site of synthesis in the hypothalamus to the neurohypophysis. Neurophysins, isolated from the posterior pituitary glands of rats,[56] porcines,[57] bovines[57,58] and humans[59] are relatively small protein molecules, containing 18 different amino acids per mole and varying in molecular weight from 9,500 to 10,500. The evidence is conclusive that there is a specific oxytocin-binding as well as a specific vasopressin-binding neurophysin,[56,57,59-62] each mole of protein binding one mole of vasopressin or oxytocin. It is of considerable interest that neurohypophyseal extracts from homozygous rats with hereditary hypothalamic diabetes insipidus (Brattleboro strain) contain normal amounts of oxytocin and oxytocin-binding neurophysin, but no vasopressin or its neurophysin.[56] The finding of hormone-specific neurophysins may contribute to a better understanding of the selective release of oxytocin and vasopressin.

Sachs and co-workers,[63] using the technique of injection of cysteine labeled with sodium sulfate S 35 into the hypothalamus, with subsequent *in vitro* isolation of vasopressin and neurophysin labeled with sodium sulfate S 35, have clearly documented that the biosynthesis of labeled vasopressin is paralleled by the formation of labeled neurophysin. Sachs and another group of associates[64] confirmed these observations, using supraoptic neurosecretory neurons of the guinea pig in organ culture, thereby suggesting that protein and hormonal peptide may arise from a common precursor. On the basis of these observations and their own studies, Burford and colleagues[56] have suggested that the relationship of each neurohypophyseal hormone and its relevant neurophysin is analogous to that of insulin and C-peptide. By this analogy, whereas in the beta-cell of the pancreatic islet, proinsulin is split to give insulin and C-peptide in the hypothalamo-neurohypophyseal cell, provasopressin and pro-oxytocin would give rise to vasopressin and vasopressin-neurophysin, and oxytocin and oxytocin-neurophysin, respectively. In 1967 Friesen and Astwood[65] suggested that these binding proteins might

be secreted into the circulation because after dehydration or administration of hypertonic saline in rats, they observed a parallel decrease in the vasopressin and neurophysin content of the extracted posterior pituitary glands. Shortly thereafter, Fawcell, Powell and Sachs[66] were able to extract neurophysin-like proteins from cavernous sinus blood following hemorrhage. Because of the development in several laboratories[61,62,67-69] of a sensitive and specific radioimmunoassay for the neurophysins, the evidence is now indisputable that neurophysin is not confined to the neurohypophysis but is released into the circulation in response to various physiologic stimuli that cause the release of vasopressin and oxytocin.

In recent years, Sachs and associates have attempted to delineate the steps in the biosynthesis of vasopressin in the hypothalamo-neurohypophyseal complex of dogs and guinea pigs by use of isotope-labeling techniques.[70,71] They have proposed a precursor model for vasopressin biosynthesis in which the biosynthesis would occur solely in the perikaryon of the neurons or nerve cell body of the supraoptic nucleus. Hormone synthesis is presumably initiated on the ribosomes via pathways common to the biosynthesis of other proteins and peptides, involving transfer RNA, messenger RNA, and so forth. However, Sachs and co-workers have proposed that the biosynthesis of vasopressin first leads to a bound, biologically inactive form (provasopressin) as part of a precursor molecule, and that the appearance of the biologically active nonapeptide occurs at a time and place removed from the initial biosynthetic events.

Conceivably, the release of the nonapeptide from the precursor molecule would take place during the formation and maturation of the neurosecretory granule. The most convincing evidence in favor of a *precursor molecule model* has come from labeling experiments carried out *in vitro* with guinea pig hypothalamo-median eminence tissue. As in the case of the *in vivo* isotope experiments, the incorporation of amino acids labeled with sodium sulfate S 35 and tritiated water into vasopressin was preceded by a lag period of about an hour. If the slices were removed from the initial incubation medium after the first hour of incubation and reincubated in fresh buffer, labeled hormone appeared under conditions which precluded further de novo peptide bond synthesis. Furthermore, the release of labeled vasopressin from a labeled precursor can take place in a cell-free system. Although the biosynthesis of labeled precursor formed during the first hour of slice incubation was inhibited by puromycin, the release of hormone from precursor was not inhibited by this drug.

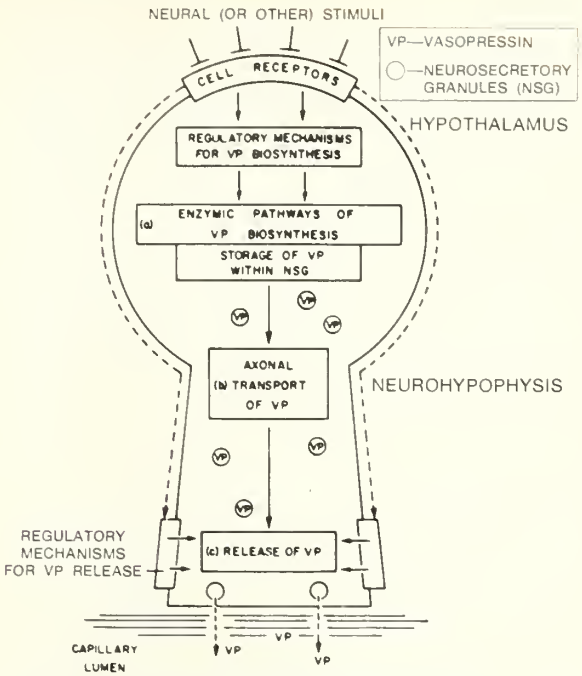


Figure 3.—Schematic representation of several intermediate stages involved in the neurosecretory function of the vasopressin-producing cells of the mammalian hypothalamo-neurohypophyseal complex. (Reproduced with permission from Sachs H, et al, *In* Stutinsky F (Ed): Neurosecretion. Berlin, Springer-Verlag, 1967.)

Figure 3 is a schematic representation of Sachs' concept of the intermediate stages involved in the neurosecretory function of the vasopressin-producing cells of the mammalian neurohypophysis. Using the radioisotope-labeling model of hormone biosynthesis, Sachs and his associates consistently found that when intact guinea pigs were deprived of water for four days before removal of neurohypophyseal tissues, the neurohypophyseal tissues incorporated two to five times more radioactivity in the newly synthesized vasopressin than in the same tissues from guinea pigs with free access to water. These findings suggest that the prolonged maintenance of nerve impulses effective in the release of vasopressin is probably also translated into sustained synthesis of the hormone. Therefore, it is likely that all stimuli which enhance release of AVP also enhance its synthesis (Table 3). It is of great interest that a species of rat (Brattleboro strain) with congenital vasopressin-

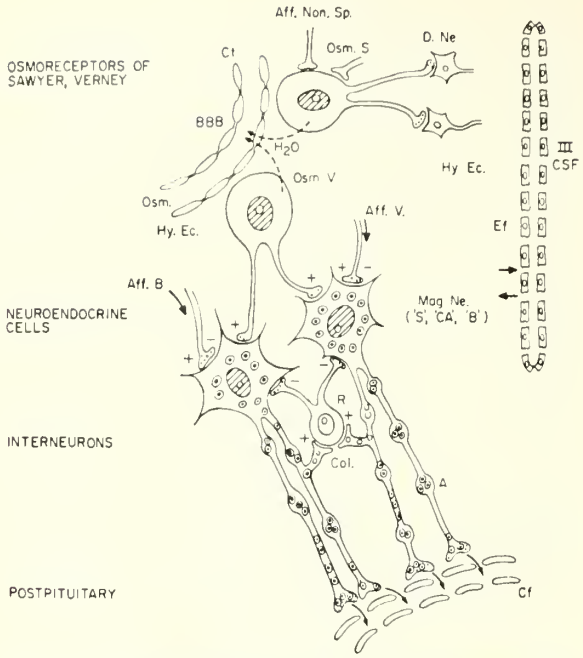


Figure 4.—Schematic drawing of the hypothalamo-neurohypophyseal system. The osmoreceptors of Verney (Osm. V.) are seen as anatomically discrete cells whose axons project to the magnocellular neurons (Mag. Ne.) in the hypothalamus. The latter cells then project to the posterior pituitary. Also shown are the osmoreceptors of Sawyer (Osm. S.) which respond to changes in osmolality as well as to noxious stimuli (Aff. V.). Axons from afferents related to behavioral stimuli (Aff. B.) are shown projecting to the magnocellular neurons. (Reproduced with permission from Hayward JN: Neurohumoral regulation of neuroendocrine cells in the hypothalamus, *In* Lederis K (Ed): Recent Studies of Hypothalamic Function. Basel, Karger, 1974, pp 166-179.)

sensitive diabetes insipidus has enormously enlarged supraoptic nuclei which, on chemical analysis, contain little or no AVP.[72] Therefore, although the hormone-forming neurons exist, some specific chemical defect prevents their synthesis of AVP.

The posterior lobe receives its blood supply from and secretes its hormone directly into the systemic circulation.

Neurophysiology of AVP Secretion

The introduction of methods capable of recording electrical activity in a single magnocellular neuron and of confirming the identity of these cells by antidromic stimulation has provided many insights into the regulation of neurosecretion.[73] Hayward and co-workers identified two distinct cell types on the basis of their response to infusion of hypertonic saline.[74] Cells with a monophasic pattern of activity that were stimulated by hyperosmolality, but were not affected by noxious stimuli, were thought to be the specific osmoreceptors of Verney that are involved in AVP release; cells with a similar specificity, but having a biphasic response pattern, were felt to be the magnocellular neurons. Alternately, cells that responded to either osmotic or noxious stimuli were designated osmoreceptors of Sawyer (Figure 4). It was speculated that these were important in the drinking and behavioral aspects of osmoregulation. In other studies, the magnocellular neurons were characterized on the basis of their firing pattern into the three following groups: silent, phasic (bursting) or continuously active. Several investigators have described modification in the firing patterns of these neurons in response to various stimuli.[75-77] This suggests that the firing pattern is, in part, a reflection of the state of activity of the neuron. There is evidence, however, that a phasic firing pattern appears to be associated with vasopressin-secreting cells and a random firing pattern with oxytocin-secreting cells.[77] Findings from such neurophysiologic studies have suggested that the specific neurons that synthesize and secrete vasopressin and oxytocin are distributed in both the supraoptic and paraventricular nuclei (Figure 5). At present, no specific functions can be attributed totally to one or the other nucleus.

Considerable progress in unraveling the physiology of AVP secretion has been made by using techniques for histochemical identification of neurosecretory neurons. The use of specific antibodies to arginine vasopressin, oxytocin and neurophysins has facilitated histologic identification not only of magnocellular (secretory) neurons, but has also resulted in delineation of additional pathways of AVP secretion in the hypothalamus. Immunohistochemical studies of hypothalamic nuclei have confirmed the intermingling of vasopressin- and oxytocin-secreting neurons in both the supraoptic and paraventricular nuclei as described above.[78] The bulk of the evidence from such studies seems to support the concept of one neurosecretory neuron producing either vasopressin and its neurophysin or oxytocin and its neurophysin.[78,79] These studies have also permitted identification of fiber tracts from the neurosecretory nuclei other than those traversing the pituitary stalk. One of these tracts projects to the zona externa of the median eminence and appears to be responsible for the very high concentration of AVP found in hypophyseal portal blood.[80] Staining in this area was greatly increased in rats

in which the adrenal glands had been excised and in which there were substantial elevations in the level of plasma AVP.[81] These observations suggest a possible role for AVP along with other hypothalamic factors in modulating corticotropin secretion. There is also evidence suggesting transport of AVP from the neurosecretory neurons to the third ventricle. Studies in our laboratory have shown that hemorrhage provokes a pronounced rise in both plasma and cerebrospinal fluid (CSF) concentrations of AVP, though to a lesser extent in the latter.[82] Such elevations did not occur after intravenous administration of AVP, which suggests that AVP was actively secreted into the CSF. This is supported by the failure of intravenously administered tritiated oxytocin to cross the blood-CSF barrier.[83] The vasopressin present in the CSF may play some role in memory consolidation. De Wied and co-workers have shown that injection of vasopressin into the third ventricle increased resistance to the extinction of a conditioned avoidance response. Memory consolidation was inhibited by injection of antivasopressin antiserum into the third ventricle.[84] They suggested that hypothalamic pathways can transport AVP to the infundibular recess of the third ventricle where it can be released into the CSF and influence memory processes related to behavioral homeostasis.

Secretion or Release of AVP

The release of AVP into the circulation, regardless of the stimulus, is dependent on depolarizing impulses arising in the supraoptic nuclei and transmitted down the axon to the hormone-storing terminal ending in the posterior lobe.[9] The *pores* in the capillaries of the neural lobe have a diameter of approximately 30 to 75 mμ or 300 to 750 A, whereas the intact neurosecretory granules in the neural lobe have a diameter of 1,600 to 5,000 A.[9] This difference in size suggests that the intact granules cannot be released as such into the circulation. However, the recent elegant electron microscopic and biochemical studies of Douglas and associates[85-88] have clearly reconciled this difference as well as defining the nature of the cellular events involved in the secretion of posterior pituitary hormones.

Earlier studies[85,89,90] suggested that on stimulation of the neurohypophysis the granules stored in the nerve ending release their contents in the form of a molecular dispersion. This dispersal allows the hormones to traverse the cytoplasm and plasma membrane of the nerve ending to

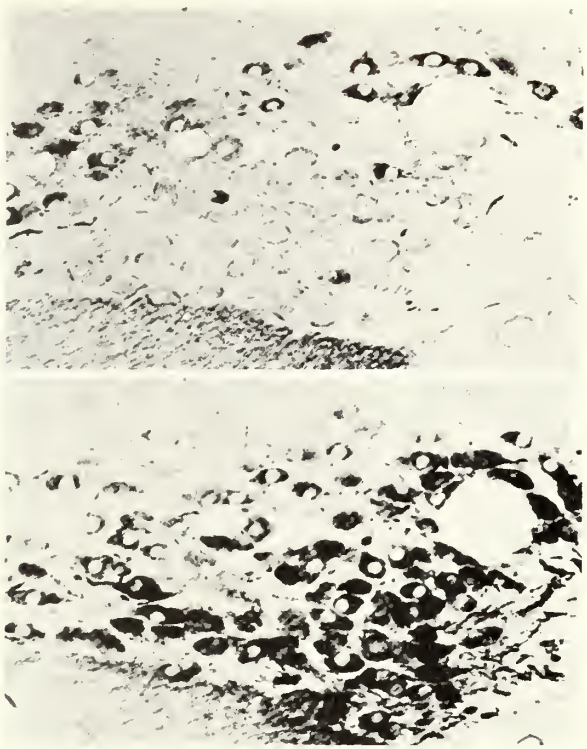


Figure 5.—Adjacent 5 μM coronal sections of the supraoptic nucleus of a normal rat reacted for oxytocin **(top)** and vasopressin **(bottom)** by the immunoperoxidase technique. Oxytocin-containing cells are concentrated in one dorsal part of the nucleus whereas vasopressin cells are found scattered throughout the nucleus with most intense staining seen in the ventral portion. Some cells are reactive for both hormones (magnification ×260). (Reproduced with permission from Zimmerman EA, Defendini R: Hypothalamic Pathways Containing Oxytocin Vasopressin and Associated Neurophysins. International Conference on the Neurohypophysis, Nov 14-19, 1976, Key Biscayne, Florida. Basel, S Karger AG, 1977.)

reach the extracellular space and from there the capillary lumen. Douglas and associates[85-88] point out that all previously proposed schemes have shared a common notion of an intracellular mechanism that is responsible for the dissociation of the hormones from their intracellular sites of storage or binding and their subsequent transport, possibly by molecular diffusion across the various plasma membrane barriers, into the circulation. These investigators[85-88] have convincingly concluded from their electron microscopic evidence that the neurosecretory granules discharge their contents directly onto the cell exterior by the process of exocytosis, beginning with fusion of the granules with the plasma membrane, and subsequent formation of an opening that communicates with the extracellular space. This mode of secre-

tion is most consistent with observations[61,62,67-69] that the hormone-binding protein neurophysin in the neurosecretory granules escapes into the circulation with the hormones when the posterior pituitary gland is stimulated.

From their excellent studies Douglas and colleagues[85-88] have further proposed that the *synaptic vesicles,* which accumulate at the nerve endings after the release of AVP and oxytocin, arise as by-products of secretion by exocytosis. These electron-lucent structures, about a fourth to a fifth the diameter of the neurosecretory granules, were called synaptic vesicles by Paley[91] because their size, appearance and distribution were similar to those of the synaptic vesicles in ordinary neurons. Paley and others suggested that they participate in hormone release. Douglas has conclusively shown that these synaptic vesicles form by inward budding endocytosis of the cell surface, mainly at the base of the exocytotic pit. The microvesicles so formed are thought to move from the membrane, aggregate and migrate centripetally in the fiber away from the terminal region of the membrane engaged in hormone extrusion. Through this mechanism, the *surplus* plasma membrane, made available by the incorporation of the membrane of the neurosecretory granule into that of the axon terminal can be disposed of.

Douglas and Poisner have shown that when the neural lobe is incubated *in vitro* and stimulated (depolarized) either electrically or by high extracellular concentrations of potassium, the actual release of the hormone is strongly calcium ion dependent.[92] Depolarization caused an increased uptake of calcium chloride Ca 45 by the neural lobe, and the secretion rate waned with the calcium content of the extracellular environment. They proposed the following steps: (1) propagation of impulse, after specific stimulus, down the neurohypophyseal stalk from supraoptic nuclei, (2) depolarization of neurosecretory axon terminals by impulses, (3) influence of calcium ion across the axon's plasma membrane and (4) activation of some calcium-dependent exocytotic process leading to hormone extrusion.

An extremely important concept regarding the release of large amounts of AVP from the neurohypophysis has been derived from the experiments of Sachs and associates.[93] Acute hemorrhagic hypotension is one of the most powerful stimuli for the immediate release of antidiuretic hormone. Within a few minutes after reducing the blood pressure of dogs to 50 mm of mercury by bleeding, there is a rapid discharge of arginine vasopressin into the blood. In the presence of a maintained stimulus of hemorrhagic hypotension, the initial secretory response is not sustained beyond the first few minutes of hemorrhage. Reinfusion of the shed blood, after 30 minutes of hemorrhage, restored the arterial pressure and the blood AVP concentration to relatively normal values. A second hemorrhage an hour later failed to raise the concentration of AVP in the blood beyond the level observed just before blood reinfusion. Direct analysis of the pituitary gland showed that the decline in the release of AVP during hemorrhage could not be attributed to exhaustion of the pituitary content of AVP. Furthermore, AVP release did not appear to be a simple function of the total hormone content of the gland. Nevertheless, this attenuation of AVP release appears to reside, in part, at the level of the pituitary. Pituitaries taken from bled dogs released much less AVP *in vitro* in response to electrical or potassium stimulation than pituitaries from animals that had not been bled. Electron microscopic studies showed that the fine structure of the neural lobes of intact and bled dogs was similar in appearance, and there was no difference in the isolated specimens. Analogous results were obtained under circumstances (carotid perfusion and section of the vagi) in which hemorrhage failed to elicit an appreciable discharge of AVP.

As a working hypothesis, it is suggested that the pool of neurohypophyseal AVP is heterogeneous and that about 10 percent to 20 percent of the total hormone content of the gland can be readily released.[93] Once this smaller pool of hormone, which can be quickly released, has been discharged, the neurohypophysis continues to release arginine vasopressin in response to appropriate stimuli, but at a greatly reduced rate. Analysis of the amount of hormone remaining in the pituitary at the end of these experiments gave values that ranged from 2,500 to 7,000 mU of vasopressin per gland. There was no apparent correlation between the amount of AVP released during the second hemorrhage and the amount of hormone found in the gland.

Quantitative Aspects of Secretion

From studies using bioassays of the hormone or its infusion at varying rates in water-load in humans,[94-96] one may conclude that in the normal ambulatory adult human, mild, sustained osmotic and nonosmotic stimuli cause the release of ap-

proximately 150 μU per minute per m^2 of AVP into the circulation. This is associated with a urinary osmolality of 500 to 1,000 mOsm per liter. During sustained dehydration (24 to 48 hours), with maximally concentrated urine, there is probably a threefold to fivefold increase in AVP release.[10-12,94,96,97] Therefore, in a 24-hour period, a normal dehydrated human (1.73 m^2) will secrete between 1 and 2 units while maintaining a maximally concentrated urine. Stimuli such as severe pain, hemorrhage or an acute decrease in cardiac output may cause a 50-fold to 100-fold increase in the rate of secretion.[8,95] For orientation it may be noted that the commercially available aqueous Pitressin contains 20 pressor units per ml of vasopressin, whereas Pitressin Tannate in Oil contains 5 pressor units per ml; 1 mg of the pure nonapeptide contains approximately 400 to 500 units of vasopressin.

The direct assay of ADH in the plasma of normal subjects in various states of hydration and the simultaneous measurement of plasma and urinary osmolality allow one to determine the relationship between concentrating ability and a given level of AVP in the circulation.[8,10,12,94,96] Segar and Moore[12] and Moore[11] plotted this relationship in a large number of subjects, showing the curve of values from undetectable levels during water diuresis to concentrations as high as 20 μU per ml during 24 to 48 hours of dehydration. They found that in the state of normal hydration, at AVP concentrations of 1.5 to 2.0 μU per ml, the urinary-to-plasma (U/P) osmolar ratios varied from 1:1 up to a high of 4:1. The sigmoid nature of their curve (Figure 6) suggests that small changes of between 1 and 3 μU per ml in plasma AVP will cause relatively large changes in the U/P osmolar ratio, whereas urinary concentrations greater than 4 μU per ml will change only slightly as circulating AVP levels approach their highest value during dehydration.[12] A similar plot of plasma AVP versus urine osmolality by Thomas and Lee[98] shows that urine osmolality varies as a linear function of log plasma AVP. This is in keeping with the log-dose response curve for AVP versus renal medullary adenylate cyclase. Therefore, from this curve and other available data,[10-12,94,96,99] it is apparent that maximal renal conservation of water can be achieved by the release of only moderate amounts of AVP. Higher rates of secretion, which would increase the plasma AVP concentration above 4 μU per ml, would not influence further the maximal concentrating capacity in the dehydrated subject. This ability to produce the most concentrated urine at rates of AVP secretion far below maximal levels is due to the increased efficiency of the vascular and countercurrent mechanisms in the kidney that are responsible for the production of the hypertonicity of the renal medulla. This intrarenal adaptation allows for a further renal conservation of water without the added need for further secretion of AVP. This is strikingly apparent in the experiments of Valtin[72] and Miller and Moses.[99] They studied rats with congenital diabetes insipidus that were unable to form AVP, yet in which progressive dehydration caused the urine osmolality to rise from its usual hypotonic level of 150 to 200 mOsm per liter to a peak of 1,100 to 1,200 mOsm per liter. Their findings

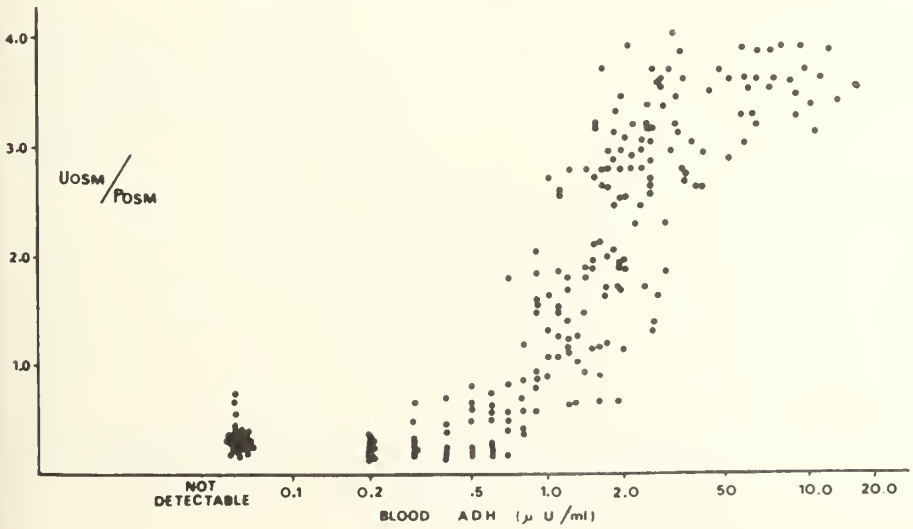


Figure 6.—Relationship between blood antidiuretic hormone concentration and urinary to plasma osmolar ratio (Uosm./Posm.) in humans; 203 pairs of data are shown. (Reprinted from Moore WW: Federation Proceedings 30:1387-1394, 1971.)

emphasize the importance of nonhormonal factors in the production of a maximally concentrated urine.

Osmotic and Nonosmotic Stimuli to AVP Secretion

Table 3 lists the known stimuli and inhibitors of the release of AVP. The final common pathway for all of these, regardless of their nature, is the nerve cell bodies of the hypothalamic supraoptic nuclei. The rate of hormone release at any moment will be controlled by the algebraic sum of the stimulating and inhibiting impulses impinging on the final common pathway. From this concept it is easy to see how the same osmotic stimulus—for example, a given increase in effective plasma osmolality—can be associated with different rates of secretion of AVP, depending on the other impulses of nonosmotic origin impinging on the supraoptic nuclei. The most common physiologic factor altering the osmolality of the blood is water depletion or water excess. The former causes a rise in the tonicity of all body fluids and cellular hydration, whereas the latter causes the reverse. The osmoreceptor neurons, in common with all body cells, share in this change in intracellular volume. The latter is probably responsible for altering the electrical activity of these neurons and, therefore, the release of AVP. If the tonicity or osmolality of all body fluids is increased by the administration of a solute such as urea that freely penetrates all body cells, no change in intracellular volume will occur and AVP release will not be stimulated. In contrast, an increase in the osmotic pressure of only 2 percent, caused by the administration of hypertonic saline during a water diuresis, will initiate the immediate release of a quantity of AVP sufficient to cause a pronounced antidiuresis (Figure 7).[100,101] On the other hand, a comparable decrease in osmotic pressure, secondary to a water load, will stop the release of AVP and produce a maximal water diuresis unless this release is maintained by some nonosmotic stimulus (Figure 8). The concept of osmotic control of AVP and its subsequent effect on the nephron, painstakingly developed in experiments in dogs by Verney and associates, was presented in Verney's outstanding Croonian lectures.[102] These represent the most fundamental work in this field and provide a lucid, exciting description of a scientific approach to clarifying a complicated physiologic feedback system.

Robertson and co-workers have plotted concomitant levels of plasma AVP and osmolality in a large number of experimental animals and showed that they were related by the function plasma AVP = k (plasma osmolality-X) where k was the slope of the regression line and X was the X intercept (Figure 9).[103,104] They proposed

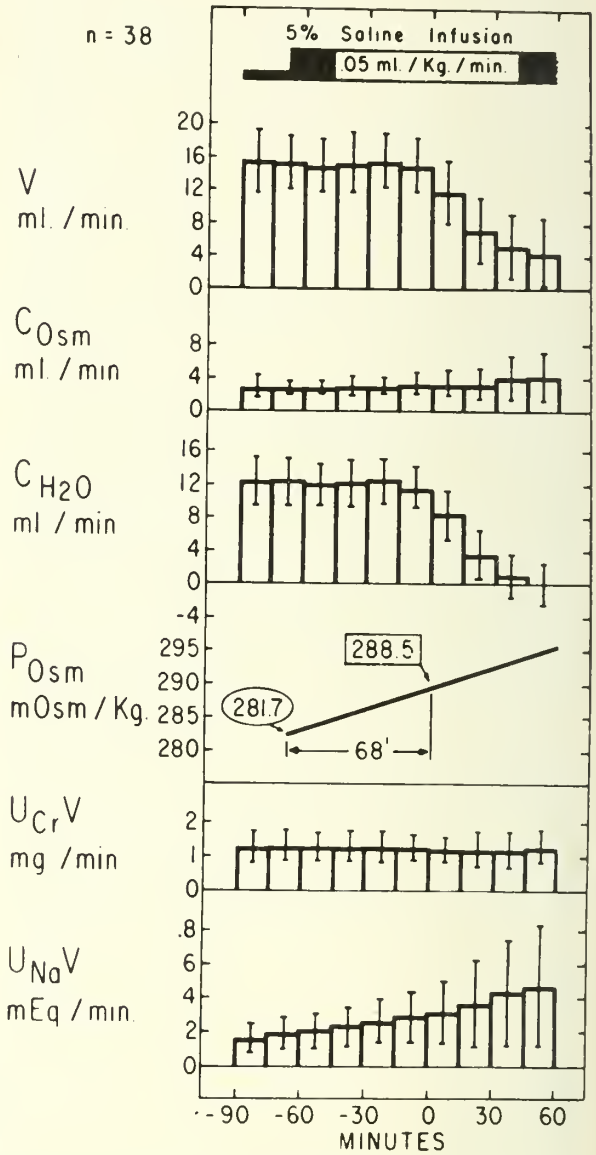


Figure 7.—Composite osmotic threshold studies on 38 normal subjects. Mean osmotic threshold in mOsm per kg of body weight is entered in rectangle and mean plasma osmolality (P_{Osm}) at the beginning of the rapid saline solution infusion is entered in ellipse. Bars and brackets represent mean ± standard deviation for urinary volume (V), osmolar clearance (C_{Osm}), free water clearance (C_{H_2O}), creatinine excretion ($U_{Cr}V$) and sodium excretion ($U_{Na}V$). Time intervals are expressed in relation to the time of the osmotic threshold. (Reproduced with permission from Moses AM, et al: Am J Med 42: 368-377, 1967.)

that the X intercept represented the "osmotic threshold" which was the critical level of osmolality at which AVP secretion would be stimulated.[103,104] The threshold concept had been proposed earlier by Moses and colleagues on the basis of the abrupt onset of a decrease in free water clearance in water-loaded subjects undergoing an infusion of hypertonic saline.[101]

Alternative theories on the osmotic control of AVP secretion have been proposed. Studies in our laboratory have suggested that instead of a discrete level of plasma osmolality above which AVP secretion would be initiated, there was rather a continuous relationship between the logarithm of plasma AVP and plasma osmolality (Figure 10).[105] This type of relationship also appears to exist between log plasma AVP and blood volume after hemorrhage. Several Scandinavian investigators have raised the question of whether a nonspecific alteration in osmolality was the factor responsible for initiation of thirst or AVP release. Eriksson and co-workers showed that intracarotid injection of hypertonic glycerol or galactose failed to produce an antidiuresis comparable to that occurring after injection of hypertonic saline or sucrose.[106] Similarly, injections of hypertonic saline into the lateral ventricles of the brain produced intense hyperdipsia and antidiuresis, while hypertonic solutions of sucrose, d-glucose or glycerol brought about increased free water clearance.[107,108] This effect of cerebroventricular infusion of sodium on thirst and antidiuresis could be augmented by concomitant administration of angiotensin II.[107] These results suggested the presence of a central, sodium-sensitive receptor near the third ventricle that was capable of controlling both thirst and AVP secretion. It appeared that angiotensin either enhanced sodium transport to the regulatory structures or that it sensitized them in some fashion. The contradictions between this hypothesis and the more general osmoreceptor hypothesis have not been resolved.

The osmotic stimulation of AVP secretion can be modified significantly by changes in volume of body fluids. Both the apparent osmotic threshold and the sensitivity (slope) of the osmolality-plasma AVP relationship were shown to be altered by modification of extracellular fluid or plasma volume (Figure 11). Hypovolemia in experimental animals resulted in lowering of the osmotic threshold, while the slope of the response relationship became steeper.[103] In later studies in humans, upright posture was shown to lower the osmotic threshold compared to the recumbent posture.[109]

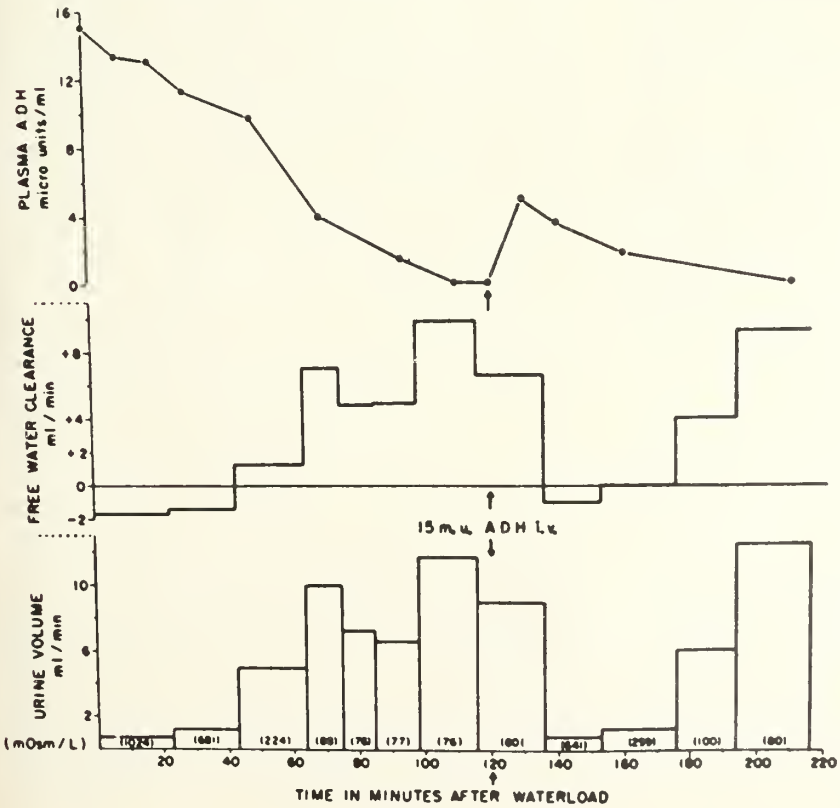


Figure 8.—Effect of a sustained oral water load (2,000 ml), followed by the intravenous injection of arginine vasopressin, on the plasma level of antidiuretic hormone (ADH) and the measurement of a maximal water diuresis. (Reproduced with permission from Czaczkes and Kleeman.[94])

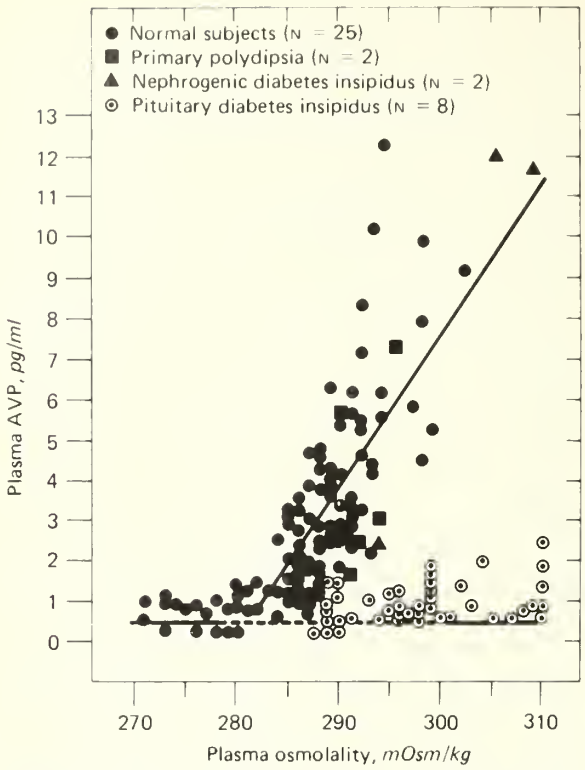


Figure 9.—Plot of plasma arginine vasopressin (AVP) and plasma osmolality in a series of normal subjects as well as in those with primary polydipsia, nephrogenic diabetes insipidus and pituitary diabetes insipidus. The best fit regression line is shown with the solid line. (Reprinted with permission from Robertson GL, Shelton RL, Athar S: The osmoregulation of vasopressin. Kidney International 10:25-37, 1976.)

In these studies there was no significant change in the slope. Intravenous infusion of angiotensin II in dogs significantly steepened the slope of the relationship between plasma osmolality and plasma AVP and served to potentiate osmotically stimulated AVP release.[110] These observations suggested an interaction of osmolar and volume factors so that AVP secretion at any moment is controlled by the algebraic sum of the stimulating and inhibiting impulses impinging on the final common pathway.

From the above, the importance of volume as well as osmolality of the body fluids in the control of the secretion of AVP is immediately apparent. A change in vascular or extracellular volume, or both, exerts its effect through baroreceptor or pressure receptor mechanisms somewhere in the circulation. In Table 3, under 2a and 2b, these receptors have been listed. In recent years, an increasing number of investigators have studied the nature of the reflex arcs activated by these receptors.*

These receptors are located in the carotid sinus, the aortic arch, the left atrium and great pulmonary veins and, probably, in the juxtaglomerular apparatus of the kidney.[16,18,22-24,113] As baroreceptors they respond as tension develops in the wall of the receptor organ rather than to the volume of blood per se; in other words, the higher the compliance (less change in mural tension for any given change in volume), the less will be the stimulation or inhibition of the receptor. The afferent limbs of the first three of these neurohumoral arcs are the ninth or glossopharyngeal nerves from the carotid sinus, the aortic nerves of the aorta, and the tenth or vagus nerve from the wall of the left atrium and great veins. Their impulses ascend from the medulla by way of the reticular formation of the midbrain and diencephalon to the supraoptic nuclei in the hypothalamus. A *decrease* in afferent impulses from these baroreceptors, caused by the stimuli listed in Table 3 brings about an *increase* in the secretion of AVP; conversly, an *increase* in the afferent impulses caused by the inhibitors listed in Table 3 results in a *decrease* of the secretion of AVP.

Section of the thoracic or cervical vagi, or denervation of the carotid sinus, will completely block these nonosmotic stimuli that lead to the release of antidiuretic hormone. Similarly, denervation of the vagus will result in a more exaggerated rise in the circulating level of AVP when a stimulus is applied that lowers pressure in the carotid sinuses as well as in the great veins of the thorax and the left atrium (Figure 12). Conversely, if the pressure in the carotid sinus is maintained despite a fall in cardiac output or blood volume, either the increment will be substantially less or the rise in the circulating level of antidiuretic hormone will be prevented entirely. Share, in his classic studies, has shown that within a few minutes after reduction of blood pressure of dogs to 50 mm of mercury by bleeding, there is a rapid discharge of vasopressin AVP into the blood.[8,112] Carotid perfusion to maintain a high pulse pressure, in a dog in which a vagotomy had been done prevented this discharge (Figure 13).

Independent of its effect on renal hemodynamics, contraction of the extracellular or plasma volume without an alteration in the tonicity of the body fluids may cause a striking release of AVP. Positive-pressure breathing, which decreases the

*References 8,9-13,16,18,22-24,26,38,111-113

intrathoracic blood volume, causes a significant release of AVP. Similarly, negative-pressure breathing with a rise in intrathoracic volume is followed by a typical water diuresis. This volume receptor, or more correctly baroreceptor, in the left atrium or great pulmonary veins, appears to be extremely sensitive to small shifts in volume or tension.

Alterations in posture have been thought to modify AVP secretion in humans. Moore and coworkers noted a significant elevation in plasma AVP in persons upon assumption of an upright posture.[11,17] However, the large changes in bioassayable AVP concentration that they observed have not been confirmed in more recent studies using radioimmunoassay. Athar and Robertson were able to show an increase in plasma AVP in persons in an upright position compared with those in a supine position only in dehydrated subjects (Figure 14).[109] They showed that upright posture influenced the relationship between plasma osmolality and plasma AVP by lowering the apparent osmotic threshold. In contrast, upright posture produced by head-up tilting caused significant elevations of plasma AVP.[114] This occurred in a biphasic pattern with a small initial increase after ten minutes of 85 degrees of tilt followed by a considerably larger increase after 45 minutes. The initial hypovolemic stimulus appeared to be due to venous pooling that led to transudation of protein-free fluid through dependent vascular beds and the later decline in plasma volume. Therefore, it appears that posture (the upright position) exerts a tonic nonosmotic stimulus to the sustained neurohypophyseal-released AVP, and, when one reclines, this stimulus is lessened, AVP secretion decreases and a mild diuresis of more dilute urine occurs. Epstein and associates have clearly shown that head-out immersion in humans creates an antigravity model whose cardiovascular (and renal) effects closely simulate those of the reclining position. In one of their studies they determined urinary AVP excretion in ten normal subjects undergoing immersion after 14 hours of overnight water restriction. The immersion resulted in a progressive

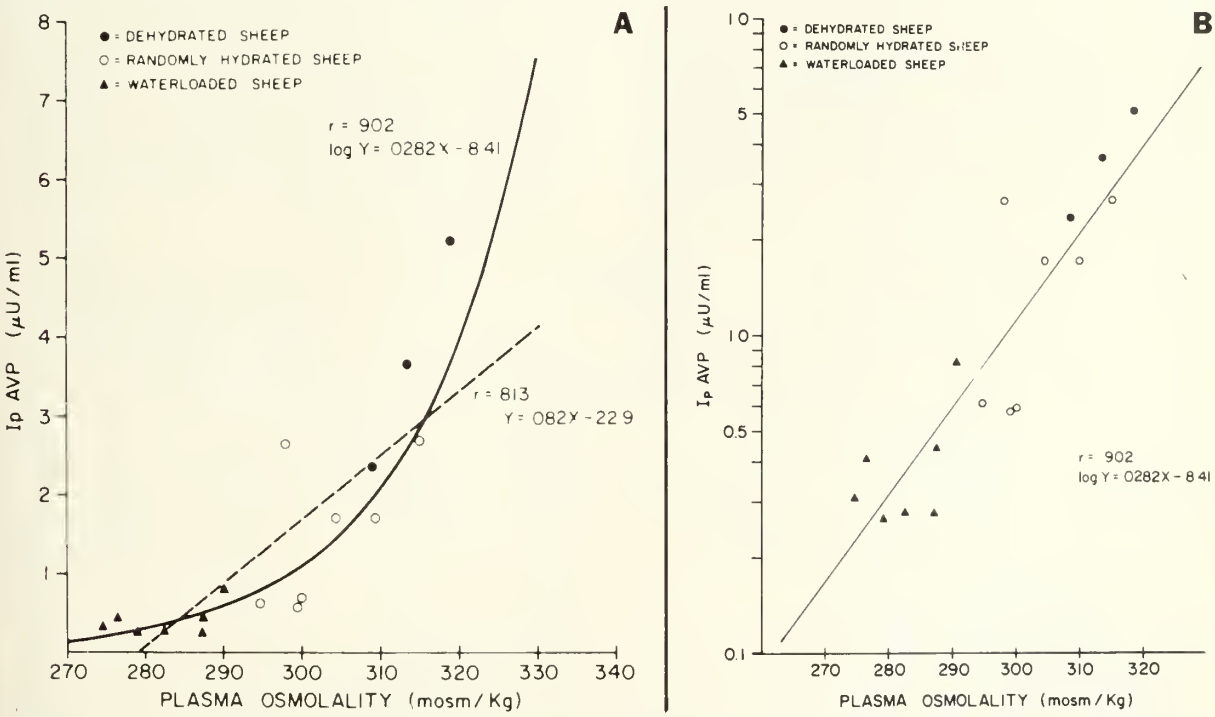


Figure 10.—A, Integrated plasma arginine vasopressin (AVP) plotted as a function of plasma osmolality (OSM) in sheep. Each point represents the mean or integrated plasma AVP concentration determined from ten samples collected at three-minute intervals. The best fit for the equation $AVP = k_1 P_{Osm} + b$ is shown with the dashed line, while the best fit for the equation $\log AVP = k_2 P_{Osm} + b$ is shown with the solid line. The logarithmic plot appears to better fit the data, particularly at the extremes of plasma osmolality. **B,** The data are replotted on a logarithmic scale. The linear relationship between log AVP and plasma osmolality is apparent when plotted in this fashion. (Reproduced with permission from Weitzman R, Fisher DA: Log linear relationship between plasma arginine vasopressin and plasma osmolality. Am J Physiol 233:E37-E40, 1977.)

decrease in AVP secretion from 80±7 to 37±6 μU per minute during the recovery hour.[115]

Zehr, Johnson and Moore[13] by carrying out detailed studies on normal, unanesthetized sheep, concluded that sensitive osmoreceptors and volume receptors (baroreceptors) exist that are involved in the regulation of AVP secretion. At the stimulus level used in their studies, neither receptor system dominated the other and, under normal circumstances, they act in concert to maintain the osmolality and volume of the extracellular fluid via their effect on AVP secretion. It is of great interest that those changes in the circulation and the volume and distribution of body fluids that stimulate the baroreceptors of the carotid sinus and left atrium (Table 3) are also the changes that bring about the release of renin from the kidneys, and thereby the production of angiotensin. If angiotension, through its direct action on hypothalamic centers, can not only stimulate thirst but can also augment the release of AVP,[16,18,22-24,113] then we must consider an additional regulatory system contributing to the modulating impulses impinging on the final common pathway, the supraoptic neurons. The tonic nature of the stimuli arising from the upright position can be seen readily by observing the increase in flow of a more hypotonic urine that almost invariably follows the assumption of a reclining position. From this, one would expect a similar diuresis to develop after the subject has retired for the night. However, this is not observed and, on the contrary, the sleeping hours are, fortunately, accompanied by a period of antidiuresis associated with an elevated plasma concentration of AVP. The mechanism responsible for the nocturnal antidiuresis obviously overrides the inhibitory stimulus of the reclining position as such. This nocturnal antidiuresis is only explained in part by the nocturnal decrease in glomerular filtration rate and solute excretion.

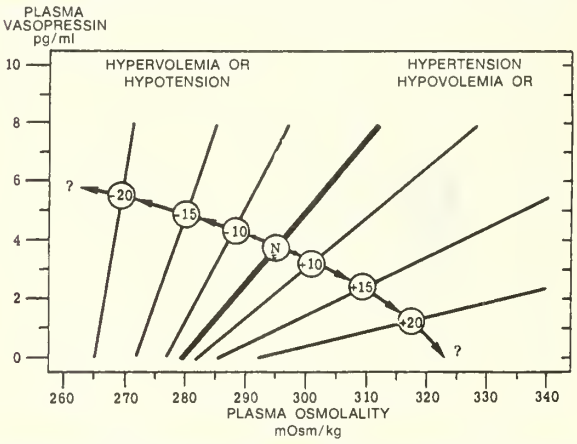
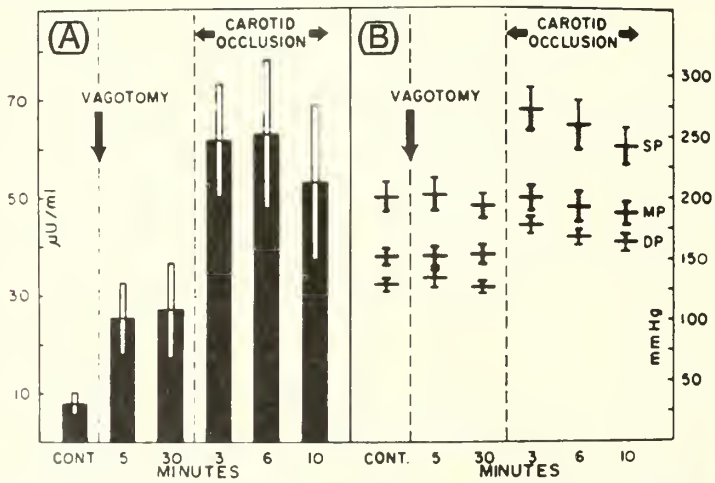


Figure 11.—Schematic diagram of the effect of alterations of blood volume or pressure on the relationship between plasma osmolality and plasma vasopressin. Decreased blood volume or blood pressure appears to enhance vasopressin release at any particular level of plasma osmolality, while increased blood volume has the opposite effect. (Reproduced with permission from Robertson GL, Shelton RL, Athar S: The osmoregulation of vasopressin. Kidney International 10:25-37, 1976.)



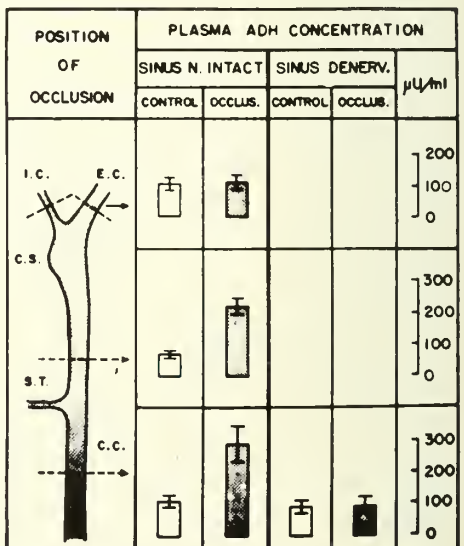


Figure 12.—**(Left)** Effect of bilateral cervical vagotomy followed by occlusion of both common carotid arteries on (A) blood titer of antiduretic hormone (ADH), and (B) femoral arterial systolic (SP), mean (MP) and diastolic (DP) pressures. Mean ± SE for seven experiments in (A), six experiments in (B).[9] **(Right)** The effect of partial ligation of the carotid artery, above and below the carotid sinus, on plasma ADH with and without sinus denervation. (Reproduced with permission from Chiens S: Proc Soc Exptl Biol Med 111:193, 1962.)

Many disease states, particularly those associated with a tendency toward sodium and water retention (such as cirrhosis, cardiac failure, nutritional edema and nephrosis) are almost invariably associated with a reversal of the normal diurnal pattern of water excretion. These disorders, accompanied by an alteration or redistribution of the vascular volume, also exaggerate the postural effect on the release of AVP. Therefore, it is probable that while exercising or in the upright position, these patients, despite their expanded extracellular volume, have a far greater release of AVP than do normal subjects. The assumption of the reclining position during the night may actually decrease the amount of AVP and lead to a nocturnal water diuresis. This is suggested in the classic studies of Borst and de Vries.[116] It is probable that the improved renal hemodynamics, reduced secretion of aldosterone and AVP, and increased circulation of the natriuretic factor[117,118] all contribute to the nocturnal polyuria that is so characteristic of the disease states mentioned above. That this reversal is also seen in states of primary or secondary adrenal insufficiency suggests a role of the glucocorticoids in the maintenance of the normal diurnal pattern. However, no clear-cut relationship has been established. One might ask why in the edematous states mentioned earlier (especially those such as con-

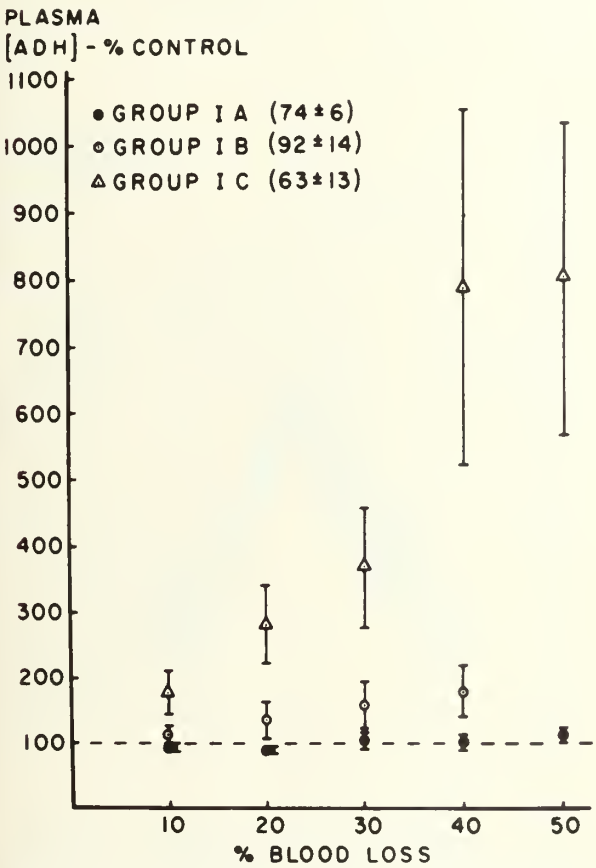


Figure 13.—Effect of hemorrhage on the concentration of antidiuretic hormone (ADH) in plasma, when the carotid sinuses were perfused with a high pulse pressure. The concentration of ADH in the first plasma sample of each experiment is taken as 100 percent. The ADH concentrations in subsequent samples are expressed as percent of the concentration in this first sample. These values are indicated on the ordinate. The abscissa is the degree of blood loss, expressed as percent of the initial blood volume, which was estimated to be 8 percent of the body weight. The lines extending above and below the symbols indicate ± SE (standard error). The figures in parentheses are the concentrations of ADH in the initial blood samples in microunits per milliliter plasma (mean ± SE). There were six experiments in group 1A, eight in group 1B, and eight in group 1C. Group 1A, control group; group 1B, perfused, with high pulse pressure during hemorrhage; group 1C, hemorrhage. (Reproduced with permission from Share.[112])

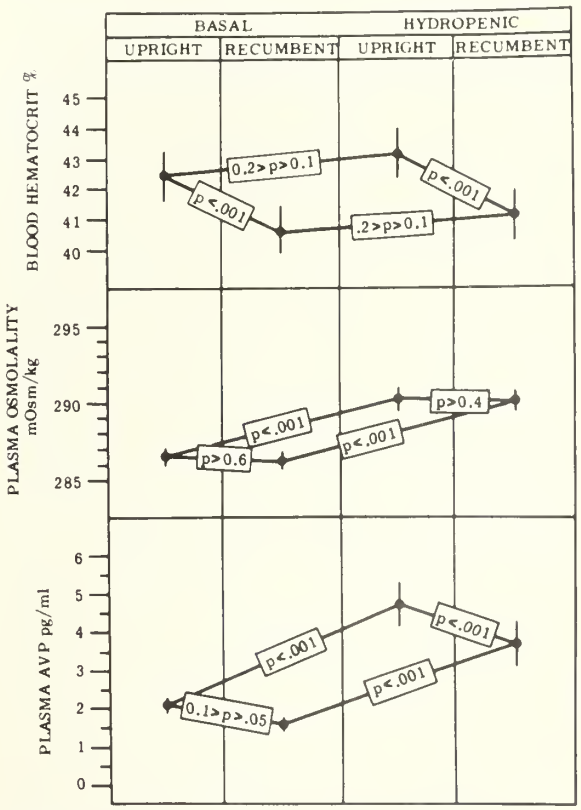


Figure 14.—The effect of dehydration and upright posture on plasma arginine vasopressin (AVP), osmolality and hematocrit in humans. A significant rise in plasma AVP in the upright posture compared with the recumbent posture was seen only when the subjects were hydropenic. (Reproduced with permission from Robertson GL, Shelton R, Athar S: The osmoregulation of vasopressin. Kidney International 10:25-37, 1976.)

gestive heart failure and cirrhosis in which blood volume is also increased) we do not see a raised osmotic threshold for AVP release as described in volume-expanded normal humans[101] and animals.[102] The most likely explanation is that impaired circulation or redistribution of blood, or both, seen in those states produce an *abnormal* response by the baroreceptors of the carotid sinus, left atrium and juxtaglomerular apparatus. Strong support for this explanation comes from the study of decompensated cirrhosis in patients by Epstein and associates using water immersion to the neck, a procedure that redistributes blood volume with concomitant central hypervolemia. This model assessed the role of *effective volume* in the impairment of sodium and water handling in patients with cirrhosis. They observed a striking rise in free water clearance (C_{H_2O}) and drop in minimal urinary osmolality (Figures 15 and 16) which were most consistent with the interpretation that both avid reabsorption of filtrate proximal to the diluting site and increased levels of AVP may participate to varying degrees in mediating the impaired water excretion accompanying cirrhosis.

It is well recognized that during very rigid sodium restriction in normal persons, the early negative salt balance during the first few days, before there is maximal renal conservation of sodium, is associated with a weight loss ranging from 0.5 to 2.0 kg. During this period, water ingested is readily excreted in isotonic proportions with salt. Further, negative salt balance and loss of extracellular volume may substantially impair water diuresis and urinary dilution. This was clearly shown in the early experiments in humans by McCance[119] and in studies in dogs and humans by Leaf and his associates (Figure 17).[120,121] Studies in our laboratory have shown that mild salt restriction for three days in normal subjects produced a statistically insignificant rise in plasma AVP. At the same time there was a significant fall in plasma tonicity.[122] In this setting, AVP secretion was inappropriate for the concomitant level of plasma osmolality. Under these conditions, volume factors were responsible for the relative elevation of plasma AVP. There is no doubt that the reduction in renal blood flow and glomerular filtration rate, the pronounced conservation of sodium and the sustained nonosmotic release of AVP all contribute to the severity of the impaired water diuresis. In many disorders associated with extensive loss of vascular or extracellular volume, the nonosmotic stimulus to the release of AVP may be of such magnitude and duration that it may override the inhibitory effect of hypo-osmolality and cellular overhydration. When this occurs, hypotonic retention of water and hyponatremia invariably follow. Although this might be considered an *inappropriate* secretion of AVP, it

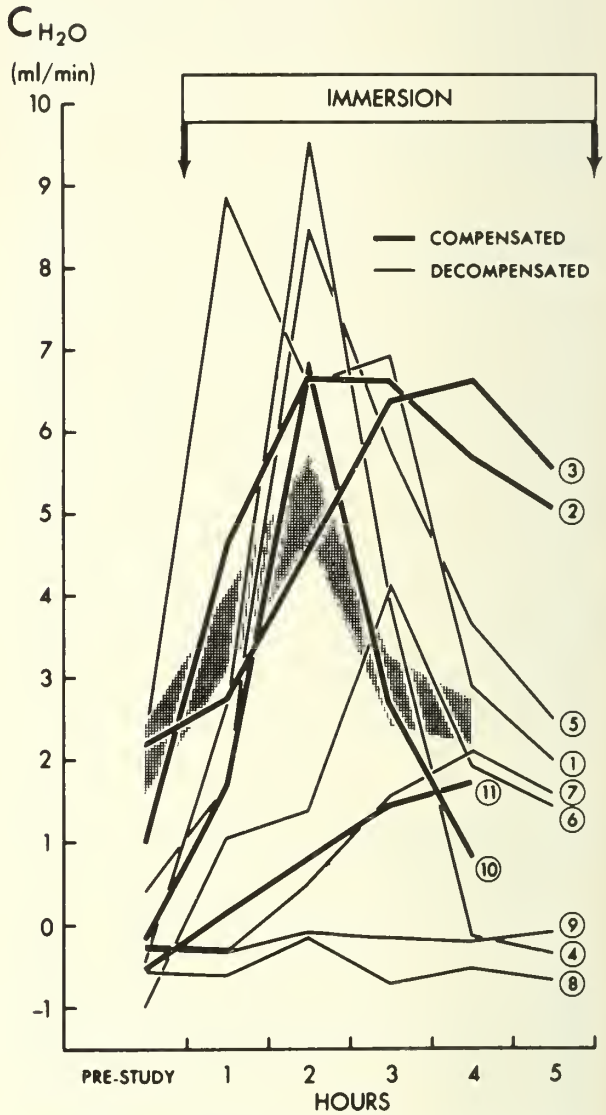


Figure 15.—Effects of water immersion following one hour of quiet sitting (prestudy) on free water clearance (C_{H_2O}) in 11 patients with alcoholic liver disease. Shaded area represents the mean ± SE for clearance for 18 normal control subjects undergoing immersion while in balance on a 150 mEq sodium diet. These controls received a water load (1,700 ml) which was twice as great as that used in the present study. Immersion resulted in a significant increase in C_{H_2O} ($P=0.01$) which equalled or exceeded that of the controls on the higher sodium intake. (Reproduced with permission from Epstein M, et al: Determinants of deranged sodium and water homeostasis in decompensated cirrhosis. J Lab Clin Med 87:832, 1976.)

is apparent that the body is merely sacrificing a small change in tonicity to buffer a larger change in volume.

Any major surgical operation, with its accompanying premedication, anesthesia, incisions, traction on viscera, decrease in blood volume and cardiac output and, finally, postoperative pain, creates a constellation of nonosmotic stimuli which lead to sustained operative and postoperative release of AVP (Figure 18). This, more than any reduction in renal blood flow or nonhormonal impairment in water excretion, is responsible for the relative or absolute impairment in water excretion in the postoperative period and the very common symptomatic or asymptomatic hyponatremia observed so frequently following surgical procedures.

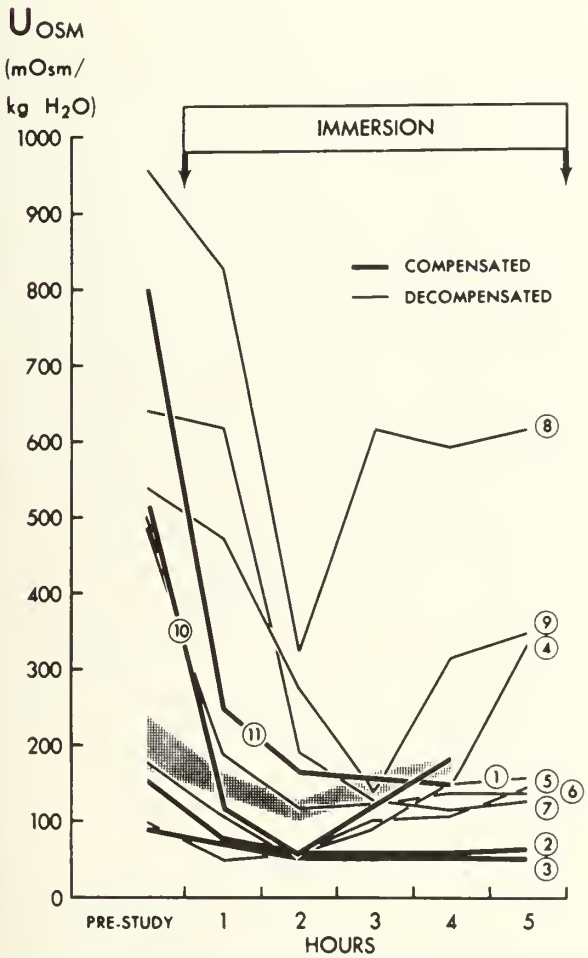


Figure 16.—Effect of water immersion following an hour of quiet sitting (prestudy) on total urinary solute concentration (U_{Osm}) in 11 patients with alcoholic liver disease. Shaded area represents the mean ± SE for U_{Osm} for 18 normal subjects undergoing immersion. These controls received a water load twice as great as that used in the present study. The urine was substantially diluted in all the patients, attaining levels of minimal U_{Osm} equal to or less than that of the controls. (Reproduced with permission from Epstein M, et al: Determinants of deranged sodium and water homeostasis in decompensated cirrhosis. J Lab Clin Med 87: 833, 1976.)

From our earlier discussion on thirst, it was evident that hypothalamic centers regulating the thirst sensation could be stimulated by impulses from the cerebral cortex. This also holds true for the release of AVP. It is well known that pain can bring about a sudden release of AVP and antidiuresis and that inappropriate antidiuresis has been observed in psychotic patients. Demerol (meperidine hydrochloride), barbiturates and morphine, all capable of stimulating AVP release when given in large amounts, may act through the baroreceptor mechanisms (Table 3) rather than by a direct pharmacologic effect on the neurohypophyseal system.

In an earlier section, we discussed the effect of various pharmacologic agents (chemicals) on the regulation of thirst and their role as possible neurohumoral transmitters in the hypothalamus. These drugs, or their analogues, also alter the release of AVP or the activity of the supraoptic neurons.[123-125] The cholinergic agents, acetylcholine, mecholyl or carbachol, when injected systemically or into the carotid artery, or applied locally to the supraoptic nuclear area, stimulate the immediate release of AVP. It is of great interest that these drugs cause a water repletion reaction, and inhibit food ingestion simultaneously.[31] Ingestion of food when water must be conserved would tend to enhance solute and water excretion. Possibly acting through these neurochemical transmitters are the effects created by warm blood perfusing the hypothalamus. Overheating of an animal or direct heating of the hypothalamus creates a sensation of thirst, a stimulation leading to the release of AVP, antidiuresis and inhibition of food intake, the water repletion reaction. However, the sensation of thirst and the release of AVP after exposure to a hot environment may also be due to stimulation of the baroreceptor mechanisms listed in Table 3. The peripheral vasodilatation and the associated redistribution of blood, with a decrease in central blood volume could stimulate the receptors. This is the interpretation of Segar and Moore,[12] who found that exposure of normal subjects for two hours at 50°C caused a four- to fivefold increase in plasma AVP. The critical importance of this

water repletion reaction to persons in a hot environment is obvious.

Recent studies have indicated that the beta-adrenergic agent isoproterenol (Isuprel), when infused systemically into normal human volunteers, anesthetized[126] and trained unanesthetized dogs,[127] all undergoing a maximal sustained water diuresis, and into rats with congenital diabetes insipidus,[128] caused an antidiuresis that was indistinguishable from that caused by AVP. However, a direct renal arterial injection of isoproterenol had no antidiuretic effect.[126,129] It is still unclear whether this beta-adrenergic antidiuresis was due primarily to the release of AVP, or to the circulatory effects of the drug, or both. The antidiuresis can be completely inhibited by the alpha-adrenergic agent norepinephrine.[127] The latter inhibits the action of antidiuretic hormone at the renal tubule[127,130] and appears to inhibit the electrical activity of the supraoptic neurons[123] and the release of AVP as well. Norepinephrine also suppresses AVP release via elevation of blood pressure and stimulation of baroreceptors. These studies on the interrelationship of catecholamines with AVP and water metabolism make it necessary, as with the renin-angiotensin system, to consider still another set of neurohumoral regulators which may influence the hypothalamic centers controlling thirst and the release of AVP.

Osmotic and Nonosmotic Inhibitors of AVP Secretion

The physiologic inhibitors of the release of AVP (Table 3) involve a reduction in intracellular osmolality (cellular dehydration), and an expansion of the plasma or extracellular fluid volume. Water diuresis with the production of a very dilute urine reflects the inhibition of the neurohypophyseal system. Cellular overhydration accompanies reduction in the osmolality of the body fluids secondary to water ingestion. When the effective osmotic pressure is reduced by 1 percent or 2 percent, expansion of intracellular fluid volume completely inhibits the release of AVP[131] unless it is maintained by some nonosmotic stimulus.

When a subject is in a reclining position and the extracellular or plasma volume is expanded

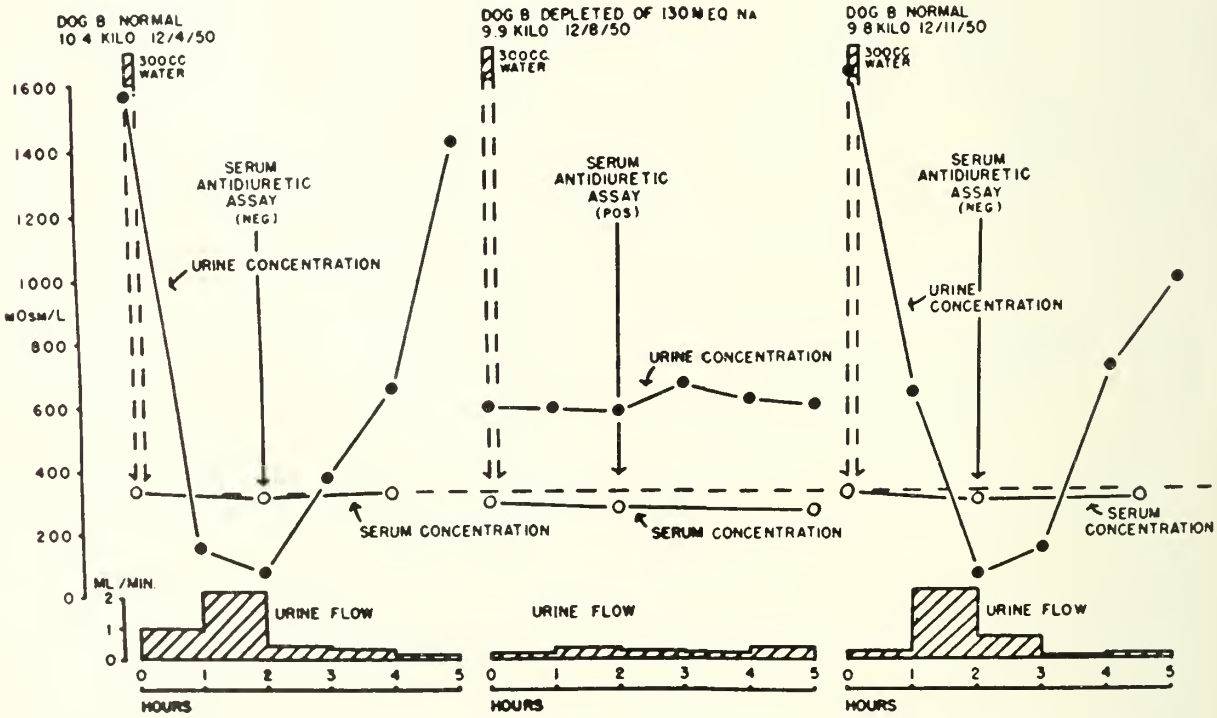


Figure 17.—The right- and left-hand portions show the diuretic pattern before and following depletion. These are entirely normal diuretic patterns. The middle section shows conversion to the abnormal antidiuretic pattern following removal of 130 mEq sodium by peritoneal dialysis. In this section, one can note a dilute serum but a hypertonic urine and failure of dilution of the urine or diuresis following water administration. Antidiuretic activity was observed in the serum during depletion but not in the controls. (Reproduced with permission from Leaf A, Mamby AR.[120])

with such solutions as isotonic saline or iso-oncotic albumin, a characteristic water diuresis occurs. These solutions, although expanding the plasma and extracellular volume, do not alter intracellular volume or the osmolality of the body fluids. It is, therefore, apparent that volume expansion as such can influence the baroreceptor impulses from the carotid sinus and left atrium (Table 3) and inhibit the renin-angiotensin system, thereby inhibiting the release of AVP.

We mentoned earlier the experiments by Moses and associates[100,101] in humans and Zehr and co-workers[13] in the unanesthetized sheep, both clearly showing that the osmotic release of AVP can be substantially decreased by previous isotonic expansion of plasma or extracellular volume or both. Further, when 400 to 500 ml of hypertonic saline (5 percent) is administered to a subject who is under the influence of a sustained positive water load (1,300 to 1,500 ml), a typical antidiuresis may not develop in spite of a pronounced hyperosmolality that causes withdrawal of water from the cells. This is due to the fact that the further expansion of the extracellular volume, which occurs in these subjects after the hypertonic salt administration, is great enough to blunt the stimulatory effect of the hyperosmolality and, therefore, decreases the release of AVP; also, on occasion, the increased excretion of sodium and osmolar clearance may be so great that despite a substantial decrease in free water clearance, indicating an approximate inhibition of the water diuresis, the rate of urine flow may not decrease.

Nonosmotic stimulation of the baroreceptors, and their inhibition of AVP release, may be produced clinically by an episode of paroxysmal atrial arrhythmia in a person with a basically normal heart. This will cause a sudden increase in cardiac output and, possibly, left atrial tension. The inhibition of AVP secretion causes a water diuresis.[132] The polyuric syndrome that may accompany sudden cardiac arrhythmias which do not significantly impair myocardial function has been known for years. We have had the opportunity to study one such polyuric patient who, despite moderate dehydration and *a rise in plasma osmolality of approximately 20 percent,* excreted a persistently hypotonic urine; no AVP could be detected in his plasma.

This case is an example of altered osmotic release of AVP caused by stimulation of the cardiac baroreceptors which, in turn, led to a nonosmotic inhibition of AVP secretion and hyperosmolality (hypernatremia). This is analogous to the effect of isotonic plasma or extracellular volume expansion on the osmotic threshold.[13,102] From these clinical and experimental observations it is possible to explain the mild hyperosmolality and hypernatremia seen in many patients with primary hyperaldosteronism. The excess mineralocorticoid secretion causes sodium retention and sustained,

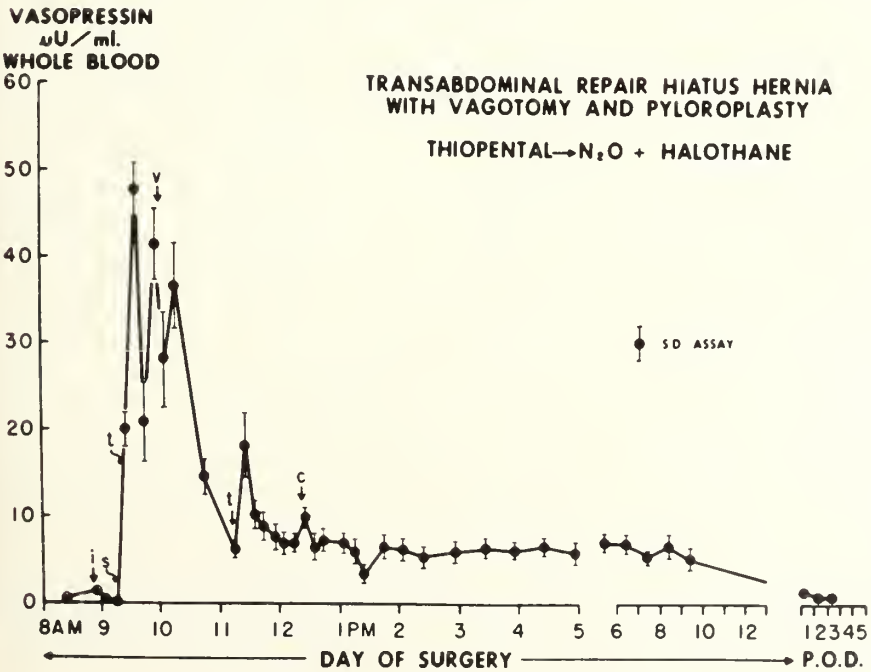


Figure 18.—Changes in blood levels of arginine vasopressin during and after a major surgical procedure. (Reproduced with permission from Zimmermann B: Surg Clin N Am 45: 310, 1965.)

steady-state expansion of the plasma and extracellular volume. The latter elevates the osmotic threshold, and hypernatremia must be present to allow the osmotic release of AVP. The hypernatremia may lead to thirst, a fairly common symptom in these patients; but when water is drunk and the plasma hyperosmolality decreases slightly, AVP secretion is again inhibited and a water diuresis ensues; thus, the hypernatremia is sustained. Such suppression of plasma AVP has been confirmed experimentally in our laboratory.[122] The administration of 9αfluohydrocortisone (Florinef) to normal volunteers produced a significant fall in plasma AVP.

The converse of the water repletion reaction which follows the administration of heat, cholinergic and beta-adrenergic agents, is the water depletion reaction, which accompanies the local hypothalamic application, or intracarotid or systemic injection of anticholinergic or alpha-adrenergic drugs such as norepinephrine. The latter may inhibit thirst and the release of AVP,[123] stimulate food intake and antagonize the action of AVP on the distal nephron.[127,130] As would be expected, exposure of an animal to cold or cooling of the blood perfusing the hypothalamus will cause a decrease in thirst, a water diuresis (the classic "cold" diuresis) and an increase in food intake. Segar and Moore[12] found that exposure of normal subjects to a temperature of 13°C for an hour caused a definite inhibition of AVP release and a fall in its concentration in the plasma. They concluded that this was due to a rise in central blood volume and blood pressure stimulating the left atrial and carotid baroreceptors.

It has been frequently shown that ethyl alcohol is a potent chemical inhibitor of the release of AVP.[9] This inhibition occurs during a rising level of alcohol in the blood after its oral or intravenous administration, although in humans, at least, the maintenance of a constant blood level does not assure the continued inhibition of AVP release. Alcohol appears to block stimuli that would ordinarily cause the release of AVP (such as hypertonic saline, reduction in blood volume or prolonged venous congestion of the lower extremities).

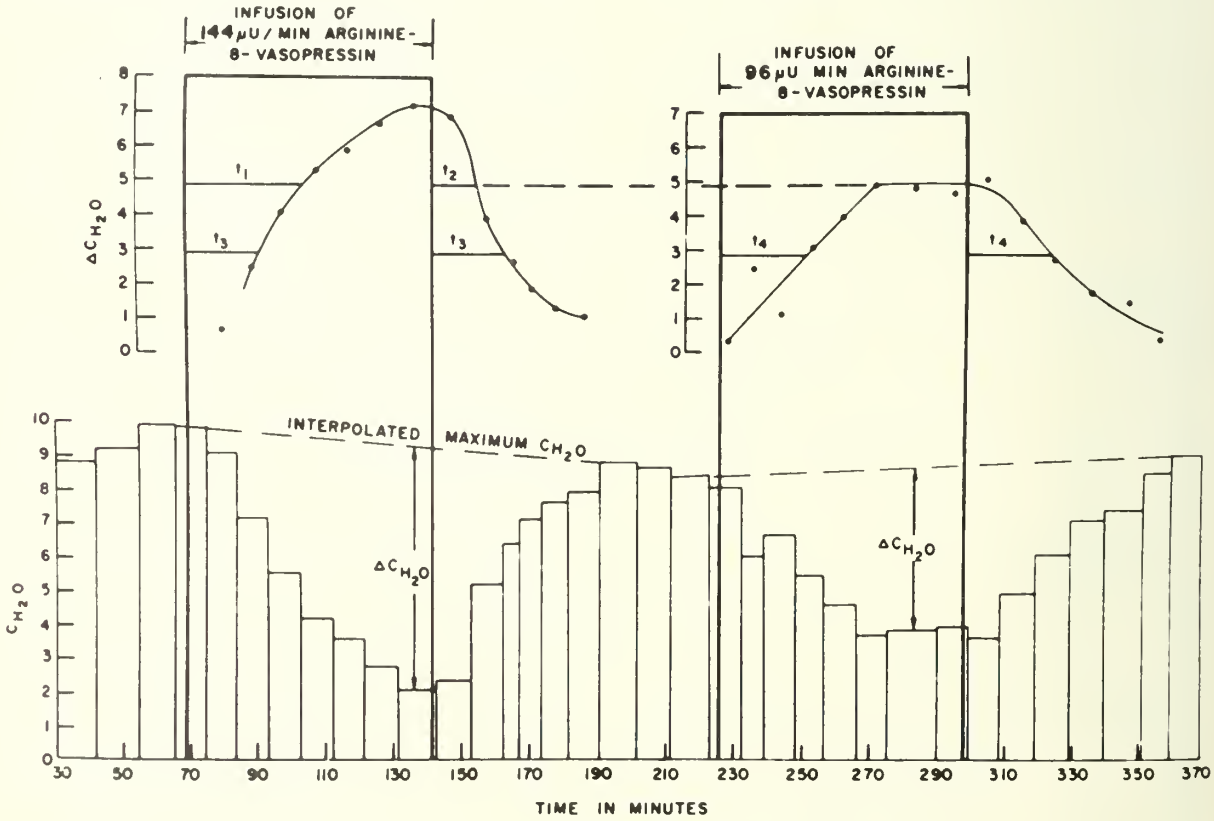


Figure 19.—A typical experiment with infusions of 144 and 96 μU per minute arginine-8-vasopressin. The C_{H_2O} is graphed for each period. The change in C_{H_2O} (ΔC_{H_2O}) is determined by the difference between the interpolated maximum C_{H_2O} and the actual C_{H_2O} for each period. (Reproduced with permission from Miller L, et al: Relative potency of arginine-8-vasopressin and lysine-8-vasopressin in humans. J Lab Clin Med 69:270-291, 1967.)

Therefore, the water diuresis that frequently follows the administration of ethyl alcohol, or the ingestion of one or two cocktails, probably represents the inhibition of certain tonic stimuli continuously reaching the neurohypophyseal nuclei. Alcohol has been used in certain clinical states (such as cirrhosis and congestive heart failure) to determine whether the observed oliguria and hypertonic urine are due to continued release of AVP. Usually, between 1 and 3 ounces of 100 proof whiskey, or its equivalent, is necessary for maximal temporary inhibition of AVP release. Unfortunately, alcohol in these amounts has not proved to be especially useful in investigation of most states associated with inappropriate or sustained nonosmotic release of AVP. Recently, diphenylhydantoin (Dilantin) has also been shown to inhibit the release of AVP in humans when administered intravenously.[133] This inhibition, as with alcohol, is quite transient and nonsustained. This also limits its usefulness in clinical states associated with inappropriate release of AVP.

Metabolism of AVP

AVP turnover can also be assessed by determining the biologic half-life of AVP *in vivo*. Such determinations have given a value of 16 to 20 minutes for the half-life of AVP.[94,95] AVP is infused intravenously into subjects undergoing a maximally sustained water diuresis. This will cause a reproducible degree of antidiuresis in a given patient under carefully controlled conditions. When the infusion is stopped, the rate of return of the urine flow to its maximal level reflects the rate of disappearance of the hormone from the circulation. An example of this is shown in Figure 19. The half-time calculated by this indirect technique[95] correlates quite well with that determined by direct bioassay of the hormone in the circulation,[94,96] but is somewhat slower than those determined by immunoassay in the separate studies cited above. Once secreted, AVP is rapidly cleared from the circulation. In humans, the plasma half-life of AVP, estimated by radioimmunoassay after pulse injection or after termination of a constant infusion of hormone, ranges from six to nine minutes.[134-136] Plasma disappearance follows a biexponential pattern with a rapid first phase and somewhat slower second phase (Figure 20). AVP is cleared in approximately equal fractions by the kidneys and liver.[96] Renal clearance persists after ureteral ligation and, thus, appears to take place largely in the postglomerular circulation.[137] Total clearance declines as the plasma concentration of AVP rises above the physiologic range.[138] These and other data have suggested a role of high-affinity plasma membrane receptors in mediating AVP clearance.[139] It is postulated that the receptors bind the biologically active hormone and facilitate its transfer from the vascular compartment to an extravascular compartment where enzymatic degradation occurs.[139]

AVP can be degraded directly in plasma at a rate of 11 percent per hour,[140] but this is relatively

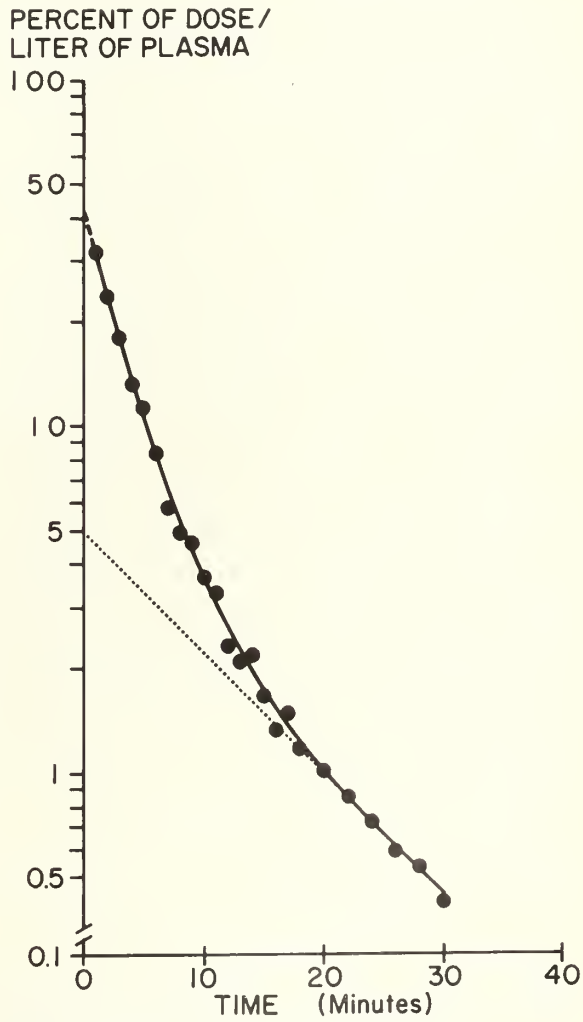


Figure 20.—Plasma arginine vasopressin measured by radioimmunoassay after pulse injection of unlabeled hormone. Two exponentials can be identified. The metabolic clearance rate (MCR) is calculated as the area under the curve and the volume of distribution as the reciprocal of the fractional dose per liter extrapolated to the time of injection. The MCR for six dogs studied in this fashion was 35.5 ± (SEM) 0.6 ml per kg of body weight per minute and the volume of distribution was 12.7 ± 0.9 percent of body weight. (From Weitzman R, Fisher DA: Unpublished data.)

insignificant compared to total body clearance. It is sufficiently great to warrant special handling of plasma samples for AVP assay. During pregnancy in humans and other primates, the placenta produces a circulating enzyme, cystine aminopeptidase (vasopressinase), which considerably augments plasma degradation. The impact of this enzyme on overall hormonal clearance is not known.

Bioassays for AVP have, for many years, been of great value in experimental and clinical studies of normal and abnormal physiology of AVP. However, they are very time consuming and lack the sensitivity of the newer and more specific radioimmunoassays.[134-137,141] The latter have permitted detection of as little as 0.2 to 0.5 units per ml of plasma. In either radioimmunoassays or bioassays, it is necessary to extract AVP from plasma to separate out substances in plasma that interfere nonspecifically with the assay. In some bioassays, it is necessary to use chemical tests such as inactivation by thioglycolate or pregnancy plasma to exclude the presence of other substances that could evoke either a pressor or antidiuretic response. In the few studies where both types of assays have been used, they generally correlate well; however, a radioimmunoassay may give higher readings due to the presence of immunologically but not biologically reactive *hormone* fragments. Such fragments may lead to an artifactual overestimation of AVP concentrations by immunoassay compared with bioassay.

Some laboratories express their data in microunits per ml, using bioassayed USP posterior pituitary extract as a standard. This material is widely available and quite stable so that results from different laboratories may easily be compared. Other laboratories use synthetic AVP as a standard and express their results in picograms per ml. Unfortunately, the potency of commercially available synthetic AVP varies greatly, as determined by bioassay, so that there may be considerable variation in the normal range in different laboratories. One picogram per ml is roughly equivalent to 0.4 units per ml.

Blood specimens for AVP measurement must be quickly chilled after collection and the plasma rapidly frozen to minimize enzymatic degradation. Even so, progressive loss of immunoreactive AVP content of plasma can be observed with prolonged freezer storage. Extraction prevents further degradation.

AVP, like many other hormones, is secreted episodically (Figure 21).[142] Thus, a solitary sample may not accurately reflect neurohypophyseal secretion in a given patient. Collection of several specimens, with pooling of the plasma before assay, has been suggested to minimize such variation.

REFERENCES

1. Kerpel-Fronius E: Clinical consequences of the water and electrolyte metabolism peculiar to infancy, *In* Ciba Foundation Colloquia on Ageing, Vol 4, Boston, Little, Brown and Company, 1958, pp 154-162

2. Schmidt-Nielsen B: The resourcefulness of nature in physiological adaptation to the environment. Physiologist 1:4-20, 1958

3. Wayner MJ: Thirst—First International Symposium on Thirst in the Regulation of Body Water. New York, The Macmillan Company, 1964

4. Andersson B: Polydipsia caused by intrahypothalamic injections of hypertonic NaCl solutions. Experimentia 8:157, 1952

5. Andersson B, McCann SM: The effects of hypothalamic lesions on the water intake of the dog. Acta Physiol Scand 35: 312-320, 1965

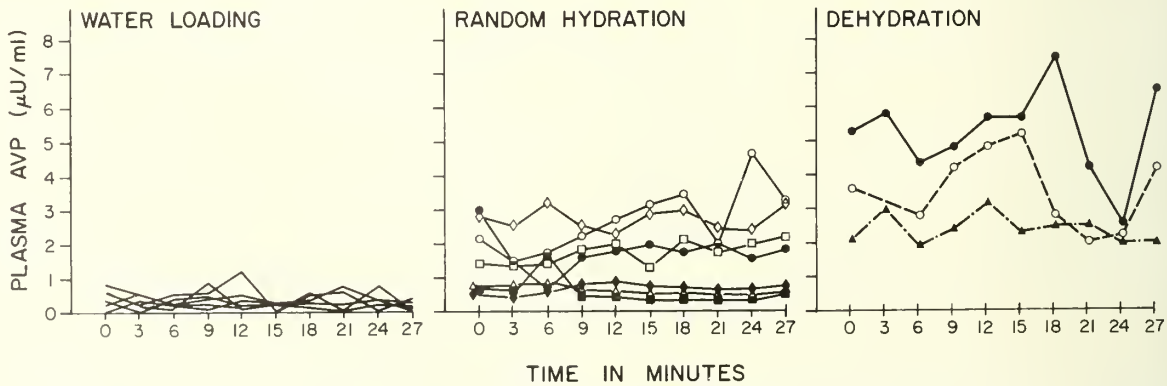


Figure 21.—Plasma arginine vasopressin (AVP) concentration sampled every three minutes for half an hour in sheep. The panel on the left shows only minimal variation in sequential samples collected in water-loaded sheep with low overall mean plasma AVP concentration. Mean AVP levels are higher in the randomly hydrated sheep (center panel) and higher still in the dehydrated animals (panel on the right). A tendency for pulsatile secretion can be observed in some of the randomly hydrated sheep and in the dehydrated sheep. (Reproduced with permission from Weitzman RE, Kleeman CR: Water metabolism and neurohypophyseal hormones, *In* Bondy P, Rosenberg L (Eds): Diseases of Metabolism. Philadelphia, WB Saunders, 1979, in press.)

6. Stricker EM: Behavioral control of intravascular fluid volume: Thirst and sodium appetite. Ann NY Acad Sci 157:553-568, 1969
7. Stricker EM: Osmoregulation and volume regulation in rats: Inhibition of hypovolemic thirst by water. Am J Physiol 217:98-105, 1969
8. Share L: Vasopressin—Its bioassay and the physiological control of its release. Am J Med 42:701-712, 1967
9. Kleeman CR, Cutler R: The neurohypophysis. Ann Rev Physiol 25:385-432, 1963
10. Nash FD: Introductory remarks—Control of antidiuretic hormone secretion. Fed Proc 30:1376-1377, 1971
11. Moore WW: Antidiuretic hormone levels in normal subjects. Fed Proc 30:1387-1394, 1971
12. Segar WE, Moore WW: The regulation of antidiuretic hormone release in man—1. Effects of change in position and ambient temperature on blood ADH levels. J Clin Invest 47:2143-2151, 1968
13. Zehr JE, Johnson JA, Moore WW: Left atrial pressure, plasma osmolality, and ADH levels in the unanesthetized ewe. Am J Physiol 217:1672-1680, 1969
14. Fitzsimons JT, Simons BJ: The effect on drinking in the rat of intravenous infusion of angiotensin, given alone or in combination with other stimuli of thirst. J Physiol 203:45-57, 1969
15. Epstein AN, Fitzsimons JT, Rools BJ: Drinking induced by injection of angiotensin into the brain of the rat. J Physiol 210: 457-474, 1970
16. Andersson B, Eriksson L, Oltner R: Further evidence for angiotensin-sodium interaction in central control of fluid balance. Life Sci 9:1091-1096, 1970
17. Fitzsimons JT: The effect on drinking of peptide precursors and of shorter-chain peptide fragments of angiotensin II injected into the rat's diencephalon. J Physiol 214:295-303, 1971
18. Andersson B, Eriksson L: Conjoint action of sodium and angictensin on brain mechanisms controlling water and salt balance. Acta Physiol Scand 81:18-29, 1971
19. Fitzsimons JT: The role of a renal thirst factor in drinking induced by extracellular stimuli. J Physiol 201:349-368, 1969
20. Severs WB, Severs AED: Effects of angiotensin on the central nervous system. Pharmacol Rev 415:448, 1973
21. Reid IA, Ramsay DJ: The effects of intracerebroventricular administration of renin on drinking and blood pressure. Endocrinology 97:536, 1975
22. Mouw D, Bonjour J-P, Malvin RL, et al: Central action of angiotensin in stimulating ADH release. Am J Physiol 220:239-242, 1971
23. Bonjour J-P, Malvin RL: Stimulation of ADH release by the renin-angiotensin system. Am J Physiol 218:1555-1559, 1970
24. Nicoll RA, Barker JL: Excitation of supraoptic neurosecretory cells by angiotensin II. Nature (New Biol) 233:172-173, 1971
25. Bonjour J-P, Malvin RL: Plasma concentrations of ADH in conscious and anesthetized dogs. Am J Physiol 218:1128-1132, 1970
26. Malvin RL: Possible role of the renin-angiotensin system in the regulation of antidiuretic hormone secretion. Fed Proc 30:1383-1386, 1971
27. Keil LC, Summy-Long J, Severs WB: Release of vasopressin by angiotensin II. Endocrinology 96:1063-1065, 1975
28. Sirois P, Gagnon DJ: Increase in cyclic AMP levels and vasopressin release in response to angiotensin I in neurohypophyses: Blockade following inhibition of the converting enzyme. J Neurochem 25:727-729, 1975
29. Uhlich E, Weber P, Elgler J, et al: Angiotensin stimulated AVP-release in humans. Klin Wochenschr 53:177-180, 1975
30. Andersson B, Larsson B: Influence of local temperature changes in the preoptic area and rostral hypothalamus on the regulation of food and water intake. Acta Physiol Scand 52:75-89, 1961
31. Grossman SP: Direct adrenergic and cholinergic stimulation of hypothalamic mechanisms. Am J Physiol 202:872-882, 1962
32. Levitt RA, Fisher AE: Anticholinergic blockade of centrally induced thirst. Science 154:520-521, 1966
33. Lehr D, Mallow J, Krukowski M: Copious drinking and simultaneous inhibition of urine flow elicited by beta adrenergic stimulation and contrary effect of alpha adrenergic stimulation. J Pharmacol Exp Ther 158:150-163, 1967
34. Leksell LG: Influence of PGE on cerebral mechanisms involved in control of fluid balance. Acta Physiol Scand 98:85, 1976
35. Andersson B, Leksell LG: Effects on fluid balance of intraventricular infusions of prostaglandin E_1. Acta Physiol Scand 93: 286, 1975
36. Yamamoto M, Share L, Shade RE: Vasopressin release during ventriculocisternal perfusion with prostaglandin E_2. J Endocrinol 71:325, 1976
37. Fitzsimons JT, Setler PE: Catecholaminergic mechanisms in angiotensin induced drinking. J Physiol 218:43P-44P, 1971
38. DeRubertis FR, Michelis MF, Beck N, et al: "Essential" hypernatremia due to ineffective osmotic and intact volume regulation of vasopressin secretion. J Clin Invest 50:97-111, 1971
39. Berl T, Anderson RG, Aisenbray GA, et al: On the mechanisms of the polyuria in potassium depletion: The role of polydipsia. Clin Res 25:136A, 1977
40. Schrub JCL, Dubuisson M, Hillermand B, et al: L'hypernatremie (Neurogenic hypernatremia—A case noted during development of a pinealoma). Sem Hop Paris 46:2084-2089, 1970
41. Sawyer WH: Active neurohypophysial principles from a cyclostome and two cartilaginous fishes. Am J Med 42:678-686, 1967
42. Sawyer WH: Evolution of neurohypophysial hormones and their receptors. Fed Proc 36:1842-1847, 1977
43. Pavel S, Goldstein R, Calb M: Vasotocin content in the pineal gland of foetal, newborn and adult male rats. J Endocrinol 66:283-284, 1975
44. Rosenbloom AA, Fisher DA: Radioimmunoassayable AVT and AVP in adult mammalian brain tissue: Comparison of normal and Brattleboro rats. Neuroendocrinology 17:354-361, 1975
45. Skowsky WR, Fisher DA: Fetal neurohypophysial arginine vasopressin and arginine vasotocin in man and sheep. Pediatr Res 11:627-630, May 1977
46. Vaughn MK, Blask DE, Vaughn GM, et al: Dose dependent prolactin releasing activity of arginine vasotocin in intact and pinealectomized estrogen-progesterone treated adult male rats. Endocrinology 99:1319, 1976
47. Chessman DW, Osland RB, Forsham PH: Suppression of the preovulatory surge of luteinizing hormone and subsequent ovulation in the rat by arginine vasotocin. Endocrinology 101:1194-1202, 1977
48. Peck JW, Blass EM: Localization of thirst and antidiuretic osmoreceptors by intracranial injections in rats. Am J Physiol 228:1501-1509, 1975
49. Van Gemert M, Miller M, Carey RJ, et al: Polyuria and impaired ADH release following medial preoptic lesioning in the rat. Am J Physiol 228:1293-1297, 1975
50. Rosenfeld M: The native hormones of the posterior pituitary glands: The pressor and oxytocic principles. Bull Johns Hopkins Hosp 66:398-403, 1940
51. van Dyke HB, Chow BF, Greep RO, et al: The isolation of a protein from pars neuralis of the ox pituitary with constant oxytocic, pressor, and diuresis inhibiting activities. J Pharmacol Exp Ther 74:190-209, 1942
52. Acher R, Chauvet J, Olivry G: Sur l'existence eventuelle d'une hormone unique neurohypophysaire—1. Relation entre l'ocytocine, la vasopressine et la proteine de van Dyke extraites de la neurohypophyse du boeuf. Biochim Biophys Acta 22:421-427, 1956
53. Acher R, Fromageot C: The relationship of oxytocin and vasopressin to active proteins of posterior pituitary origin—Studies concerning the existence or non-existence of a single neurohypophysial hormone, *In* Heller H (Ed): The Neurohypophysis. London, Butterworth and Company, Ltd, 1957, pp 34-37
54. Ginsburg M, Ireland M: The role of neurophysin in the transport and release of neurohypophysial hormones. J Endocrinol 35:289-298, 1966
55. Dean CR, Hope DB: The isolation of neurophysin I and II from bovine pituitary neurosecretory granules separated on a large scale from other subcellular organelles. Biochem J 106:565-573, 1968
56. Buford GD, Jones CW, Pickering BT: Tentative identification of a vasopressin-neurophysin and an oxytocin-neurophysin in the rat. Biochem J 124:809-813, 1971
57. Cheng KW, Friesen HG: Isolation and characterization of a third component of porcine neurophysin. J Biol Chem 246:7656-7665, 1971
58. Hollenberg MD, Hope DB: The isolation of the native hormone binding proteins from bovine posterior pituitary lobes. Biochem J 106:557-564, 1968
59. Cheng KW, Friesen HG: The isolation and characterization of human neurophysin. J Clin Endocrinol Metab 34:165-176, 1972
60. Ranch R, Hollenberg MD, Hope DB: Isolation of a third bovine neurophysin. Biochem J 115:476-479, 1969
61. Robinson AG, Zimmerman EA, Frantz AG: Physiologic investigation of posterior pituitary binding—Proteins neurophysin I and neurophysin II. Matabolism 20:1148-1155, 1971
62. Robinson AG, Zimmerman EA, Engleman EG, et al: Radioimmunoassy of bovine neurophysin: Specificity of neurophysin I and neurophysin II. Metabolism 20:1138-1147, 1971
63. Sachs H, Fawcett CP, Takabatake Y, et al: Biosynthesis and release of vasopressin and neurophysin. Rec Progr Horm Res 24: 447-491, 1969
64. Sachs H, Goodman R, Osinchak J, et al: Supraoptic neurosecretory neurons of the guinea pig in organ culture—Biosynthesis of vasopressin and neurophysin. Proc Natl Acad Sci USA 68: 2782-2786, 1971
65. Friesen HG, Astwood EB: Changes in neurohypophysial proteins induced by dehydration and ingestion of saline. Endocrinology 80:278-287, 1967
66. Fawcett CP, Powell AE, Sachs H: Biosynthesis and release of neurophysin. Endocrinology 83:1299-1310, 1968
67. Cheng KW, Friesen HG: Physiological factors regulating secretion of neurophysin. Metabolism 19:876-890, 1970
68. Cheng KW, Friesen HG: A radioimmunoassay for vasopressin binding protein, neurophysin. Endocrinology 88:608-619, 1971
69. Legros JJ, Frachimont P: The radioimmunoassay of bovine neurophysin: Evidence of a cross-reaction with a substance in human plasma, *In* Kirkham KE, Hunter WM (Eds): Radioimmunoassay Methods. Edinburgh, Churchill Livingstone, 1971, p 98
70. Sachs H, Portanova R Haller EW, et al: Cellular processes concerned with vasopressin biosynthesis, storage, and release, *In* Stutinsky F (Ed): Neurosecretion—Fourth International Symposium on Neurosecretion. Berlin, Springer-Verlag OHG, 1967, p 146
71. Sachs H: Biosynthesis and release of vasopressin. Am J Med 42:687-700, 1967
72. Valtin H: Hereditary hypothalamic diabetes insipidus in rats (Brattleboro strain)—A useful experimental model. Am J Med 42:814-827, 1967
73. Cross BA, Dyball REJ, Dyer RG, et al: Endocrine neurons. Rec Progr Horm Res 31:243-294, 1975
74. Hayward JN: Neural control of the posterior pituitary. Ann Rev Physiol 37:191-210, 1975
75. Arnauld E, Vincent JD, Dreifus JJ: Firing patterns of hypothalamic supraoptic neurons during water deprivation in the monkey. Science 185:535-537, 1974
76. Wakerley JB, Poulain DA, Dyball REJ, et al: Activity of phasic neurosecretory cells during hemorrhage. Nature 258:82-84, 1975

77. Dreifus JJ, Harris ME, Tribollet E: Excitation of phasically firing hypothalamic supraoptic neurons by carotid occlusion in rats. J Physiol 257:337-354, 1976
78. Zimmerman EA, Robinson AG: Hypothalamic neurons secreting vasopressin and neurophysin. Kidney Int 10:12-24, 1976
79. Zimmerman EA: Localization of hypothalamic hormones by immunocytochemical techniques, *In* Martini L, Ganong WF (Eds): Frontiers in Neuroendocrinology, Vol 4. New York, Ravin Press, 1976
80. Zimmerman EA, Carmel PW, Husain MK, et al: Vasopressin and neurophysins—High concentrations in monkey hypophysial portal blood. Science 182:925-927, 1973
81. Seif SM, Huellmante AB, Shullman M, et al: Neurophysin and vasopressin in the plasma and hypothalamus of adrenalectomized and normal rats. Endocrinology 96:186A, 1975
82. Vorherr H, Bradbury MWB, Hoghoughi M, et al: Antidiuretic hormone in cerebrospinal fluid during endogenous and exogenous changes in its blood level. Endocrinology 33:246, 1968
83. Zaid SM, Heller H: Can neurohypophysial hormones cross the blood-cerebrospinal fluid barrier? J Endocrinol 60:195-196, 1974
84. Van Wimersma Greidanus TB, Dogterom J, de Wied D: Intraventricular administration of antivasopressin serum inhibits memory consolidation in rats. Life Sci 16:637-644, 1975
85. Douglas WW, Nagasawa J, Schultz R: Electron microscopic studies on the mechanism of secretion of posterior pituitary hormones and significance of microvesicles ("synaptic vesicles"): Evidence of secretion by exocytosis and formation of microvesicles as a by-product of this process, *In* Heller H, Lederis K (Eds): Memoirs of the Society for Endocrinology—Subcellular Organization and Function in Endocrine Tissues. London, Cambridge University Press, 1971, pp 353-378
86. Nagasawa J, Douglas WW, Schultz RA: Ultrastructural evidence of secretion by exocytosis and of "synaptic vesicle" formation in posterior pituitary gland. Nature 227:407-409, 1970
87. Nagasawa J, Douglas WW, Schultz RA: Micropinocytotic origin of coated and smooth microvesicles ("synaptic vesicles") in neurosecretory terminals of posterior pituitary glands demonstrated by incorporation of horseradish peroxidase. Nature 232: 341-342, 1971
88. Douglas WW, Nagasawa J, Schult RA: Coated microvesicles in neurosecretory terminals of posterior pituitary glands shed their coats to become smooth "synaptic" vesicles. Nature 232:340-341, 1971
89. Barer R, Heller H, Lederis K: The isolation, identification and properties of the hormonal granules of the neurohypophysis. Proc R Soc Lond (Biol) 158:388-416, 1963
90. Gerschenfeld HM, Tramezzani JH, DeRobertis E: Ultrastructure and function in the neurohypophysis of the toad. Endocrinology 66:741-762, 1960
91. Paley S: The fine structure of the neurohypophysis, *In* Waelsch H (Ed): Ultra-Structure and Cellular Chemistry of Neural Tissue, Progress in Neurobiology, Vol 2. New York, Paul B. Hoeber, Inc, 1957, pp 31-49
92. Douglas WW, Poisner AM: Stimulus-secretion coupling in a neurosecretory organ—The role of calcium in the release of vasopressin from the neurohypophysis. J Physiol (London) 172: 1-18, 1964
93. Sachs H, Share L, Osinchak J, et al: Capacity of the neurohypophysis to release vasopressin. Endocrinology 81:755-770, 1967
94. Czaczkes JW, Kleeman CR: The effects of various states of hydration and the plasma concentration on the turnover of antidiuretic hormone in mammals. J Clin Invest 43:1625-1640, 1964
95. Miller L, Fisch L, Kleeman CR: Relative potency of arginine-8-vasopressin and lysine-8-vasopressin in humans. J Lab Clin Med 69:270-291, 1967
96. Lauson H: Metabolism of antidiuretic hormones. Am J Med 42:713-744, 1967
97. Sawyer WH: Biological assays for neurohypophysis principles in tissues and in blood, *In* Harris GW, Donovan T (Eds): The Pituitary Gland, Vol 3. Berkeley, The University of California Press, 1966, pp 288-306
98. Thomas TH, Lee MR: The specificity of antisera for the radioimmunoassay of arginine vasopressin in human plasma and urine during water loading and dehydration. Clin Sci Molec Med 51:525-536, 1976
99. Miller M, Moses AM: Radioimmunoassay of urinary antidiuretic hormone with application to study of the Brattleboro rat. Endocrinology 88:1389-1396, 1971
100. Moses AM, Streeten DHP, Streeten MD: Differentiation of polyuric states by measurement of responses to changes in plasma osmolality induced by hypertonic saline infusions. Am J Med 42: 368-377, 1967
101. Moses AM, Miller M, Streeten DHP: Quantitative influence of blood volume expansion on the osmotic threshold for vasopressin release. J Clin Endocrinol 27:655-662, 1967
102. Verney EB: The antidiuretic hormone and the factors which determine its release. Proc R Soc Lond (Biol) 135:25-106, 1947-1948
103. Robertson GL, Mahr EA, Athar S, et al: Development and clinical application of a new method for the radioimmunoassay of arginine vasopressin in human plasma. J Clin Invest 52:2340-2352, 1973
104. Dunn FL, Brennan TJ, Nelson AE, et al: The role of blood osmolality and volume in regulating vasopressin secretion in the rat. J Clin Invest 52:3212-3219, 1973
105. Weitzman RE, Fisher DA: Log linear relationship between plasma arginine vasopressin and plasma osmolality. Am J Physiol 233:E37-E40, 1977
106. Eriksson L, Fernandez O, Olsson K: Differences in the antidiuretic response to intracarotid infusions of hypertonic solutions in the conscious goat. Acta Physiol Scand 83:554-562, 1971
107. Andersson B, Eriksson L: Conjoint action of sodium and angiotensin on brain mechanisms controlling water and salt balances. Acta Physiol Scand 81:18-29, 1971
108. Eriksson L: Effect of lowered CSF sodium concentration on the central control of fluid balances. Acta Physiol Scand 91: 61-68, 1974
109. Robertson GL, Athar S: The interaction of blood osmolality and blood volume in regulating plasma vasopressin in man. J Clin Endocrinol Metab 42:613-620, 1976
110. Shimizu K, Share L, Claybaugh JR: Potentiation by angiotensin II of the vasopressin response to an increased plasma osmolality. Endocrinology 93:42-50, 1973
111. Gauer OH, Henry JP: Circulating basis of fluid volume control. Physiol Rev 43:423-481, 1963
112. Share L: Role of peripheral receptors in the increased release of vasopressin in response to hemorrhage. Endocrinology 81:1140-1146, 1967
113. Travis RH, Share L: Vasopressin-renincortisol interrelations. Endocrinology 89:246-253, 1971
114. Davies R, Slater JDH, Forsling ML, et al: The response of arginine and plasma renin to postural change in normal man with observations on syncope. Clin Sci Molec Med 51:267-274, 1976
115. Epstein M: Cardiovascular and renal effects of head out water immersion in man. Circ Res 39:619-628, 1976
116. Borst JGG, deVries LA: The three types of "natural" diuresis. Lancet 2:1-6, 1950
117. Cirksena WJ, Dirks JH, Berliner RW: Effect of thoracic cava obstruction in response of proximal tubule sodium reabsorption to saline infusion. J Clin Invest 45:179-186, 1966
118. Rector FC Jr, Sellman JC, Martinez-Maldonado M, et al: The mechanisms of suppressions of proximal tubular reabsorption by saline infusions. J Clin Invest 46:47-56, 1967
119. McCance RA: Experimental sodium chloride deficiency in man. Proc R Soc Lond (Biol) 119:245-268, 1936
120. Leaf A, Mamby AR: An antidiuretic mechanism not regulated by extracellular fluid. J Clin Invest 31:60-71, 1952
121. Leaf A, Frazier HS: Some recent studies on the actions of neurohypophysial hormones. Progr Cardiovasc Dis 4:47-64, 1961
122. Weitzman R, Farnsworth L, MacPhee R, et al: The effect of opposing osmolar and volume stimuli on plasma arginine vasopressin (pAVP) in man. Mineral Elec Metab 1:43-47, 1978
123. Barker JL, Crayton JW, Nicoll RA: Noradrenaline and acetylcholine response of supraoptic neurosecretory cells. J Physiol 218:19-32, 1971
124. Berl T, Cadnaphornchai P, Harbottle JA, et al: Mechanisms of suppression of vasopressin during alpha adrenergic stimulation with norepinephrine. J Clin Invest 53:219-227, 1974
125. Shimamoto K, Miyahara M: Effect of norepinephrine infusion on plasma vasopressin levels in normal human subjects. J Clin Endocrinol Metab 43:201-204, 1976
126. Schrier RW, Lieberman R, Ufferman RC: Mechanism of antidiuretic effect of beta-adrenergic stimulation. J Clin Invest 51:97-111, 1972
127. Klein LA, Liberman B, Laks M, et al: Interrelated effects of antidiuretic hormone and adrenergic drugs on water metabolism. Am J Physiol 221:1657-1665, 1971
128. Levi J, Grinblat J, Kleeman CR: Effect of isoproterenol on water diuresis in rats with congenital diabetes insipidus. Am J Physiol 221:1728-1732, 1971
129. Gill JR Jr, Casper ACT: Depression of proximal sodium reabsorption in the dog in response to renal beta-adrenergic stimulation by isoproterenol. J Clin Invest 50:112-118, 1971
130. Fisher DA: Norepinephrine inhibition of vasopressin antidiuresis. J Clin Invest 47:540-547, 1968
131. Baldes EJ, Smirk FH: The effect of water drinking, mineral starvation and salt administration on the total osmotic pressure of the blood in man, chiefly in relation to the problems of water absorption and water diuresis. J Physiol 82:62-74, 1934
132. Wood P: Polyuria in paroxysmal tachycardia and paroxysmal atrial flutter and fibrillation. Br Heart J 25:273-282, 1963
133. Fichman MP, Vorherr H, Kleeman CR, et al: Diuretic-induced hyponatremia. Ann Intern Med 75:853-863, 1971
134. Skowsky WR, Rosenbloom AA, Fisher DA: Radioimmunoassay measurement of arginine vasopressin in serum: Development and application. J Clin Endocrinol Metab 38:278-287, 1974
135. Beardwell CG, Geelen G, Palmer HM, et al: Radioimmunoassay of plasma vasopressin in physiological and pathological states in man. J Endocrinol 67:189-202, 1975
136. Morton JJ, Padfield L, Forsling ML: A radioimmunoassay for plasma arginine vasopressin in man and dog—Application to physiological and pathological states. J Endocrinol 65:411-424, 1975
137. Rabkin R, Young J, Crofton J, et al: The renal handling of arginine vasopressin. Clin Res 25:62A, 1977
138. Levi J, Rosenfeld S, Kleeman CR: Inactivation of arginine vasopressin by the isolated perfused rabbit kidney. J Endocrinol 62:1-10, 1974
139. Weitzman RE, Fisher DA: Arginine vasopressin metabolism in dogs—I: Evidence for a receptor-mediated mechanism. Am J Physiol 235:E591-E597, Dec 1978
140. Wilson KC, Weitzman RE, Fisher DA: Arginine vasopressin metabolism in dogs—II: Modeling and system analysis. Am J Physiol 235:E598-E605, Dec 1978
141. Robertson GL Mahr EA, Athar S, et al: Development and clinical application of a new method for the radioimmunoassay of arginine vasopressin in human plasma. J Clin Invest 52:2340-2352, 1973
142. Weitzman RE, Fisher DA, Di Stefano JJ IV, et al: Episodic secretion of AVP. Am J Physiol 233:E32-E26, 1977

Specialty Conference

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Moderators

GLENN D. BRAUNSTEIN, MD
WILLIAM D. ODELL, MD, PhD

Discussants

WILLIAM D. ODELL, MD, PhD
DANIEL D. FEDERMAN, MD

This Symposium was held at the 26th Annual Meeting of the Pacific Coast Fertility Society, Scottsdale, Arizona, October 18-22, 1978.

Symposium on Adolescent Gynecology and Endocrinology

Part I: Physiology of Sexual Maturation and Primary Amenorrhea

Physiology of Sexual Maturation

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Introduction and Pubertal Staging

IN MOST MAMMALS, sexual maturation appears to be a continual process beginning near or before birth and continuing until the process is complete. For example, sexual maturation occurs in rats at 35 to 45 days of age and in cattle at 12 to 13 months of age as a result of a continual process commencing near birth. In sharp contrast, sexual maturation in higher primates (rhesus monkeys, baboons and humans) follows a prolonged preadolescent or prepubertal period which lasts several years. During this preadolescent period, the hypothalamic-pituitary-gonadal system is quiescent and inhibited, and does not respond to perturbation as would the system in adults or in other animals. This control of gonadal function during this prepubertal period of higher primates, which lasts from about 6 months to 9 to 12 years of age in humans, is very poorly understood. Once this period is completed, the changes of puberty (sexual maturation) occur in humans over three to five years' time in both sexes and in about 95 percent of children between ages 9 to 17 years. For humans, it is most convenient to discuss sexual maturation by using a classification scheme for various stages of pubic hair, breast and genital changes. Those most commonly used were described by Tanner[1] and are shown in Figures 1 to 4 and described in Tables 1 to 3. Pubic hair stages, illustrated in Figures 2 and 3 for boys and girls, are described in Table 1. Genital stages for boys are described in Table 2. Stages of breast development are described in Table 3. These classifications of various stages of puberty are useful in following the process and relating degree of maturation to hormonal changes. We shall return to these stages later. Let us first discuss our knowledge of maturation in animal systems.

Control of Sexual Maturation in Rodents, Cattle and Pigs

A number of laboratories have measured luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in rats,[2,3] mice,[4] cattle[5-7] and miniature pigs[8] during sexual maturation. Figures 5 and 6 show the data from our laboratory in maturing rats. In female rats (Figure 5), FSH falls throughout sexual maturation; LH initially falls slightly and then is constant from 21 to 37

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ABBREVIATIONS USED IN TEXT

FSH = follicle-stimulating hormone
GnRH = gonadotropin releasing hormone
HCG = human chorionic gonadotropin
LH = luteinizing hormone

days of age. In male rats (Figure 6), FSH is high at 5 to 10 days of age, rises slightly to 40 days of age and then also falls as sexual maturation proceeds. LH, initially high at 10 days, falls sharply and then slowly rises between 20 and 90 days of age. FSH and LH changes in mice and hamsters are somewhat similar to those in rats. Figure 7 shows LH and FSH in maturing bulls. Note that in this species, LH and FSH are constant at relatively low levels whereas testicular function, as reflected in blood testosterone changes, increases steadily. LH and FSH concentrations are also constant from birth to sexual maturation in pigs.

The most widely believed hypothesis of the cause of sexual maturation has been that of a changing hypothalamic sensitivity to the negative feedback effects of gonadal steroids. In this hypothesis, the immature hypothalamus is inhibited by very small amounts of gonadal steroids. As the organism matures, sensitivity of the hypothalamus to negative feedback diminishes and the result is increasing LH or FSH, or both, which in turn was believed to stimulate increased gonadal steroid production. However, the data in Figures 5 through 7 show that in rodents, cattle and pigs this hypothesis cannot be correct. We have pre-

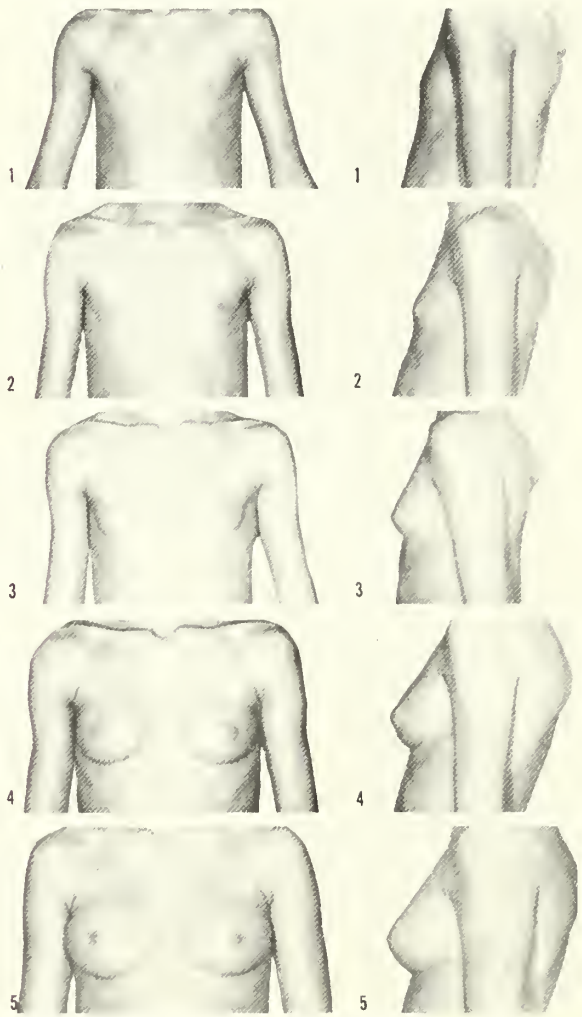


Figure 1.—Standards for breast development ratings. Numbers indicate stages. (Reproduced by permission from Tanner.[1])

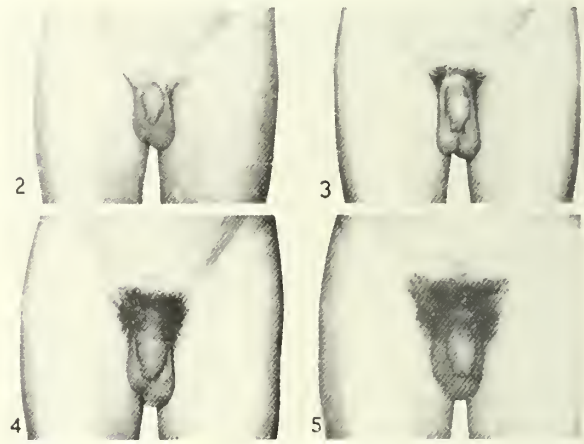


Figure 2.—Standards for pubic hair ratings in boys. Numbers indicate stages. (Reproduced by permission from Tanner.[1])

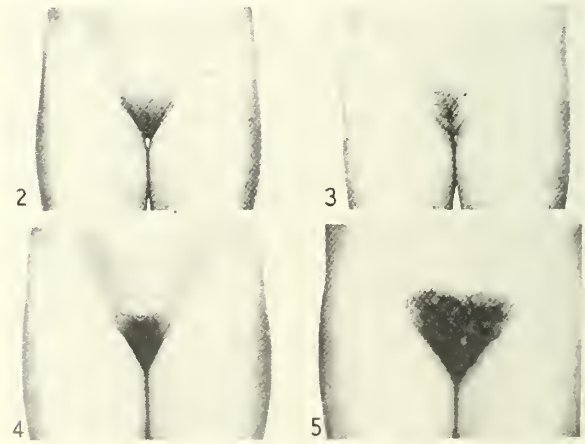


Figure 3.—Standards for pubic hair ratings in girls. Numbers indicate stages. (Reproduced by permission from Tanner.[1])

viously reviewed[2] the studies in animals, made before the availability of LH and FSH measurements, upon which this hypothesis was based.

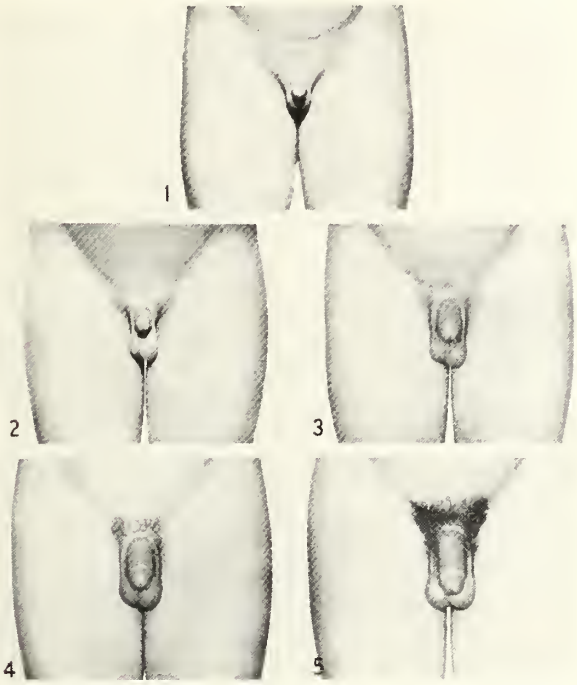


Figure 4.—Standards for genital maturity in boys. Numbers indicate stages. (Reproduced by permission from Tanner.[1])

TABLE 1.—*Pubertal Hair Stages for Girls and Boys*

Stage 1—Preadolescent. The vellus over the pubes is not further developed than that over the abdominal wall; that is, there is no pubic hair.

Stage 2—There is sparse growth of long, slightly pigmented downy hair, straight, or slightly curled, chiefly at the base of the penis or along the labia.

Stage 3—The hair is considerably darker, coarser and more curled. It spreads sparsely over the junction of the pubes.

Stage 4—Hair is now adult type, but the area covered is still considerably smaller than in adults. There is no spread to the medial surface of the thighs.

Stage 5—The hair is adult in quantity and type with distribution of the horizonal (or classically feminine) pattern. Spread is to the medial surface of the thighs, but not up the linea alba or elsewhere above the base of the inverse triangle (spread up the linea alba occurs late and is rated stage 6).

Stage 6—In about 80 percent of men and 10 percent of women, the pubic hair spreads further into one of the patterns called sagittal, acuminate or disperse, but this takes some time to occur after stage 5 has been reached. When it does happen, the pubic hair is rated 6, a terminology which retains the uniform rating for males and females on the 5-point scale and, at the same time, places this longer-term development beyond the more concentrated period of adolescence.

If one castrates rats at 10 or 12 days of age,[2] or cattle at any age before sexual maturation,[5] gonadotropin concentrations rise in blood, usually reaching levels similar to those after castration in adults. From these data we reason the hypothalamic-pituitary-gonadal system is intact before maturation in these animals. Similarly, LH and FSH may be suppressed by exogenous estrogen or androgens before maturation in rats and sensitivity does not correlate with sexual maturation. As we will explain later, the human hypothalamic-pituitary-gonadal system is not intact (or responsive as we know it to be in adults) before puberty. During this prepubertal period, in humans and higher primates, castration does not increase concentrations as it does after sexual maturation.

Interestingly, in the rats we have studied,[11] gonadal response to exogenous LH does change with sexual maturation. Figure 8 shows the percent increase in blood testosterone following a single injection of two doses of purified LH given to male rats throughout maturation. The dose of LH was constant in all rats, adjusted for body

TABLE 2.—*Genital Stages for Boys*

Stage 1—Preadolescent. Testes, scrotum and penis are about same size and shape as in early childhood.

Stage 2—Scrotum and testes are slightly enlarged. The skin of the scrotum is reddened and changed in texture. There is little or no enlargement of the penis at this stage.

Stage 3—Penis is slightly enlarged, at first mainly in length. Testes and scrotum are further enlarged than in stage 2.

Stage 4—Penis is further enlarged, with growth in breadth and development of glans. Testes and scrotum are further enlarged than in stage 3; scrotal skin is darker than in earlier stages.

Stage 5—Genitalia are adult in size and shape.

TABLE 3.—*Stages of Breast Development*

Stage 1—Preadolescent. Elevation of the papilla only.

Stage 2—Breast bud stage. Elevation of the breast and the papilla as a small mound. Areolar diameter is enlarged over stage 1.

Stage 3—Breast and areola are both enlarged and elevated more than in stage 2, but with no separation of their contours.

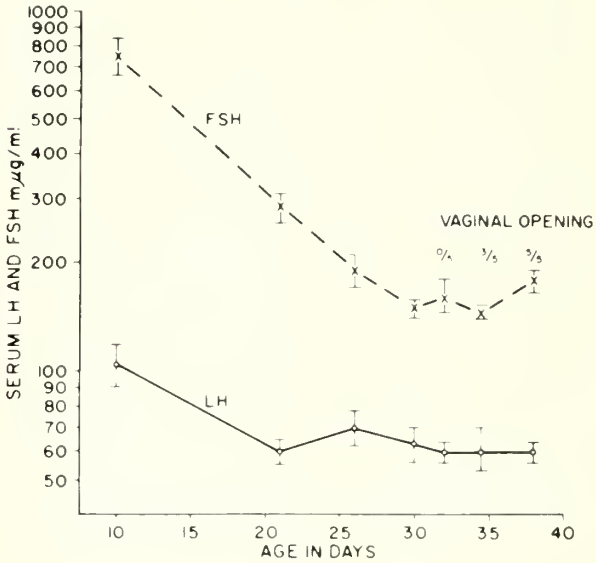
Stage 4*—Areola and papilla form a secondary mound projecting above the contour of the breast.

Stage 5*—Mature stage. The papilla only projects, with the areola recessed to the general contour of the breast.

*The stage 4 development of the areolar mound does not occur in some girls; in probably a quarter it is absent and in a further quarter slight. Furthermore, when it does occur it may persist well into adulthood. Thus stages 4 and 5 are not distinct in all girls.

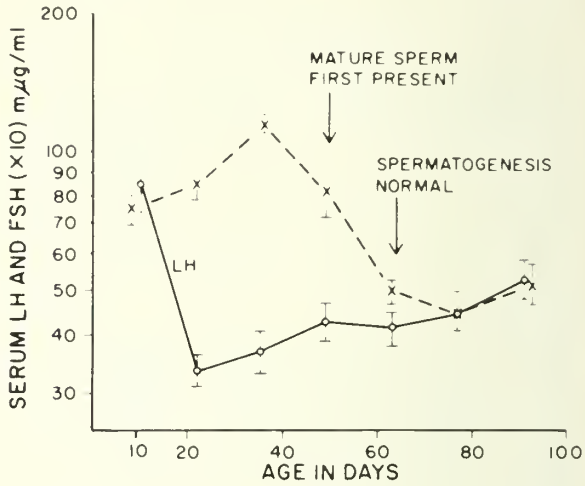
weight. Note that at 10 days of age, two doses of LH increased testosterone by 200 percent; these doses increased testosterone by 600 percent at 21 days, and at 41 days 10 μg of LH per 100 grams of body weight increased testosterone by about 800 percent and 30 μg increased testosterone by about 1,700 percent. Thus, a constant dose of LH produced progressively greater testicular response as the animal matured. These increases in LH response are correlated with increases in LH receptor populations. Figure 9 shows these data.

The cause or control of these changing LH-



(a)

Figure 5.—Serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in female rats from 10 to 40 days of age. At 34 days of age, vaginal opening had occurred in 60 percent and at 38 days in 100 percent of animals. After vaginal opening, only serum samples obtained in diestrus were included. (Reproduced by permission from Swerdloff et al.[9])



(b)

Figure 6.—Serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in male rats from 10 to 91 days of age. Mature sperm were first noted at age 49 days; spermatogenesis appeared to be complete by 63 days. (Reproduced by permission from Swerdloff et al.[9])

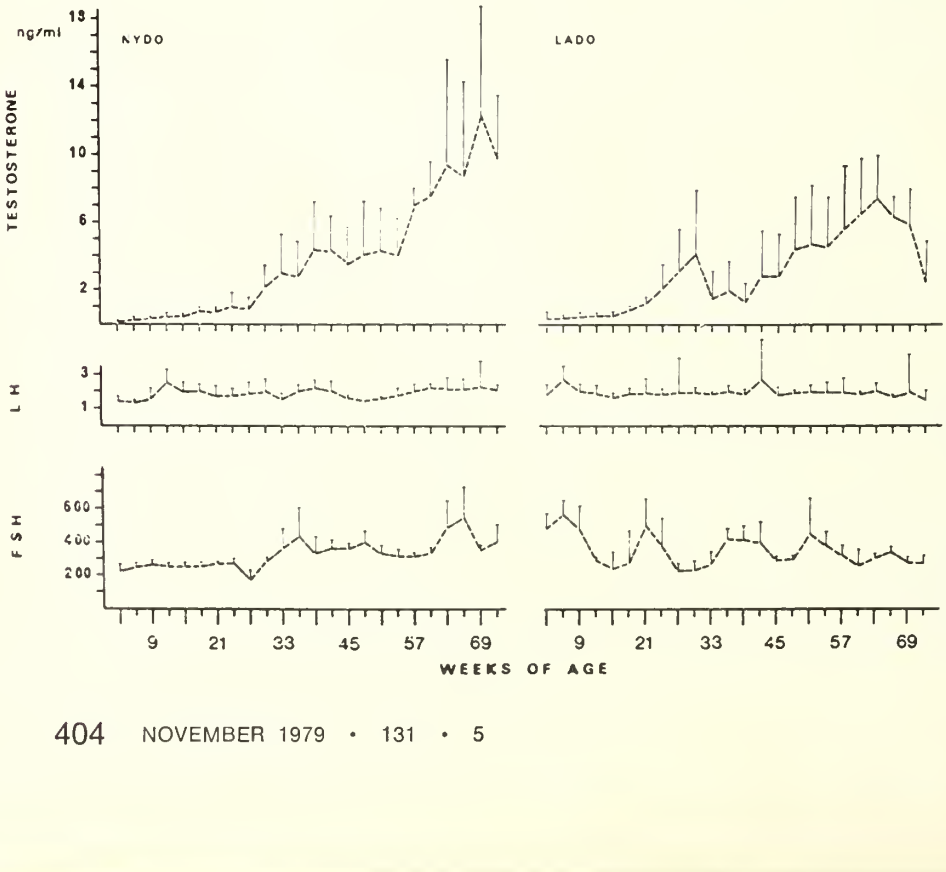


Figure 7.—Concentrations of testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (mean value±SD for each three-week sampling period) in peripheral plasma in bulls from birth through maturation. (Reproduced by permission from Karg et al.[7])

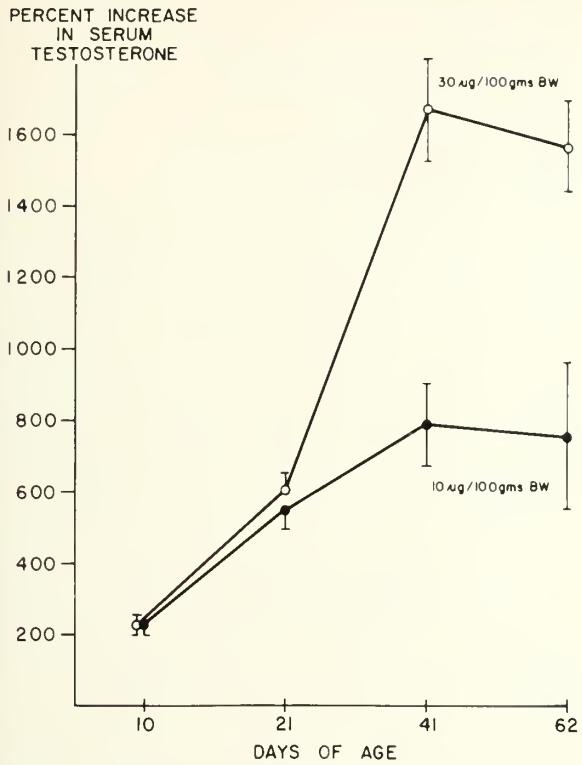


Figure 8.—Percent increase in serum testosterone plotted against age of animals for two doses of luteinizing hormone (LH): o—o, 30 µg per 100 grams of body weight. A single dose of LH was given intraperitoneally at the ages shown: •—•, 10 µg per 100 grams of body weight. Blood testosterone was measured one hour later. The time response was maximal. Note that for both doses of LH, the percent increase in blood testosterone increased with age. (Reproduced by permission from Odell et al.[12])

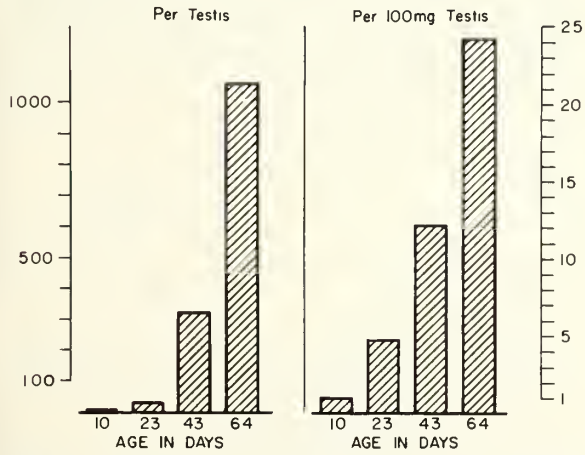


Figure 9.—Luteinizing hormone (LH) receptors determined by Scatchard plot analyses in intact male rats at different ages. The results indicate that the relative receptor populations, expressed either per testis (left) or per testis weight (right), increase progressively with sexual maturation. (Reproduced by permission from Odell and Swerdloff.[2])

receptor populations is also complex. We have tested a variety of hormones, and find that FSH is most potent in inducing LH receptor formation and sensitivity to LH. Figure 10 shows some of these data. In these studies, 21-day-old immature rats were hypophysectomized. On the day of hypophysectomy, either saline (control) or FSH injections were begun and continued for five days. At the fifth day, a constant dose of LH (15µg per 100 grams of body weight) was given and the increment in blood testosterone measured. Note that there exists a dose response relation between FSH dosage and response to the constant dose LH;

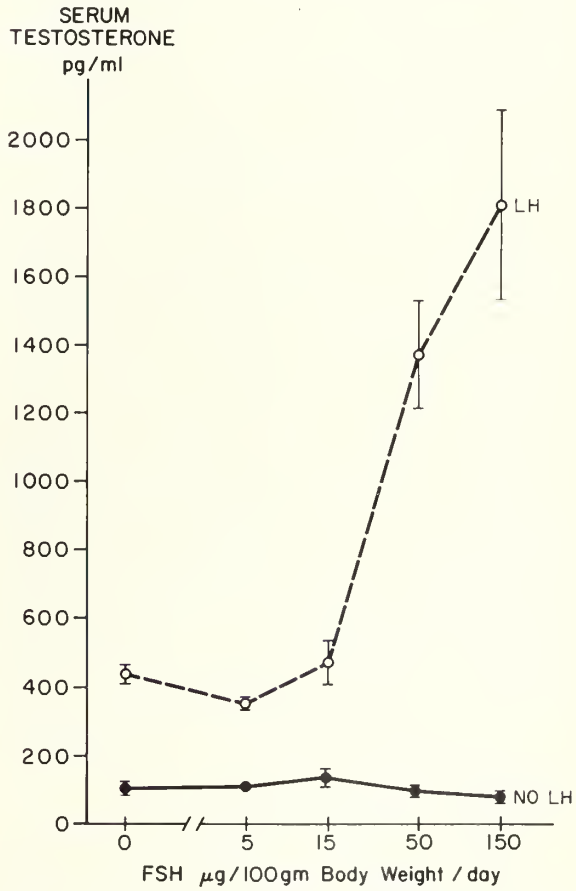


Figure 10.—Follicle-stimulating hormone (FSH) induction of testosterone response to a single dose of luteinizing hormone (LH). In this study, 21-day-old male rats were hypophysectomized and begun immediately on a five-day course of follicle-stimulating hormone (FSH) treatment in the doses stipulated. On the sixth day, a single dose of LH (15 µg) was administered and blood was obtained one hour later for serum testosterone determination (o—o). Control animals (•—•) received either saline or FSH, but no LH. FSH produced a dose-related enhancement of testosterone response to constant doses of LH. (Reproduced by permission from Odell and Swerdloff.[2])

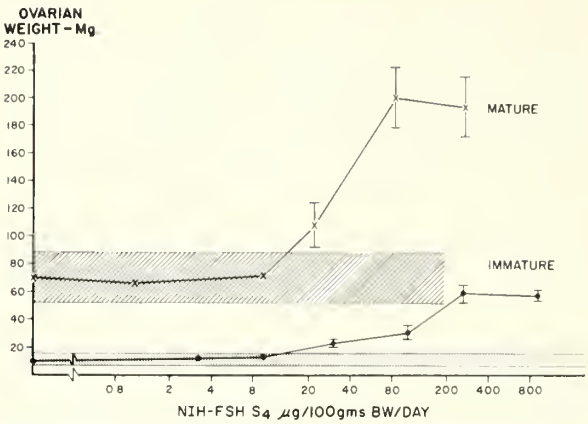


Figure 11.—Effects of varying doses of follicle-stimulating hormone (FSH) on ovarian weight in sexually immature (21-day-old) and sexually mature (45-day-old) female rats. Note that the minimal effective dose was identical in both groups. In contrast to FSH, luteinizing hormone (LH) produces no detectable response by uterine weight increment, nor prostate weight increment in immature female and male rats, respectively, when given five days following hypophysectomy. (Reproduced by permission from Odell et al[12])

that is, FSH induced responsiveness to LH. These data have led us to postulate: *FSH induces LH receptor formation which in turn permits increasing gonadal response to LH.*[2,11,12] *This action is a major determinant of sexual maturation in nonprimates.*

In other studies we have shown that gonadal sensitivity to FSH is identical in immature and mature male and female animals. Figure 11 shows these data for females. In addition to FSH, certain other hormones can modify sensitivity to LH and probably LH receptor populations. The second most potent hormone (after FSH) is growth hormone. Interestingly, prolactin appears to have little effect in this regard.

In summary, we postulate the following concerning the process of sexual maturation in rodents, cattle, sheep and pigs:

- The process occurs throughout the period of birth (or possibly before birth) to completion of sexual maturation.
- The gonadal response to LH changes during maturation is parallel with changing LH receptor populations.
- FSH (and growth hormone) induce LH receptor formation.
- Changing negative feedback sensitivity to gonadal steroids is not involved.
- LH and FSH, initially high in blood in rats, fall as gonadal steroids rise in response to LH action. In cattle, LH and FSH are constant as gonadal steroids rise indicating probably a change in negative feedback sensitivity.

Sexual Maturation in Higher Primates and Man

As indicated during the introduction, humans have a prolonged prepubertal or preadolescent period. During this period, the hypothalamic-pituitary-gonadal axis is not intact or *engaged* as it is in the sexually mature. This is shown by two observations: (1) very low levels of gonadal steroids are associated with very low levels of LH and FSH and (2) castration during this period produces a very small or no rise in blood LH

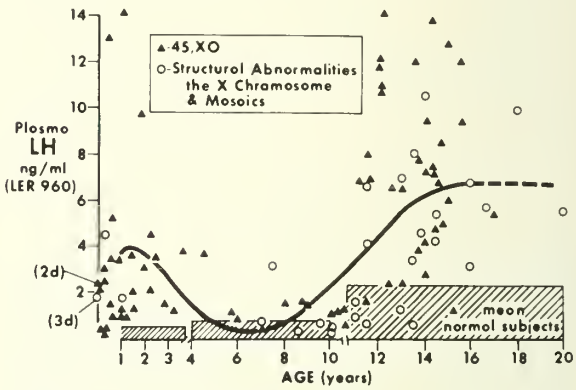


Figure 12.—Plasma luteinizing hormone (LH) concentrations in agonadal girls between birth and 20 years of age. The shaded areas designate data from eugonadal girls. Note that LH is high during the first 2 to 3 years of age, falls and is normal or nearly normal between 4 and 11 years of age, but then rises to castrate concentrations after the usual age of puberty. (Reproduced by permission from Grumbach.[26])

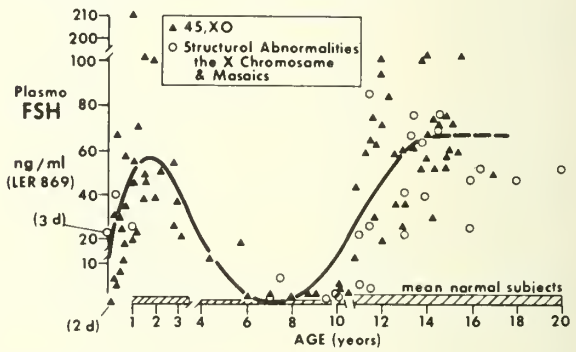


Figure 13.—Plasma follicle-stimulating hormone (FSH) concentrations in agonadal girls between birth and 20 years of age. The shaded areas designate data from eugonadal girls. Note that FSH is high during the first 2 to 3 years of age, falls and is normal or nearly normal between 4 and 11 years of age, but then rises to castrate concentrations after the usual age of puberty. (Reproduced by permission from Grumach.[26])

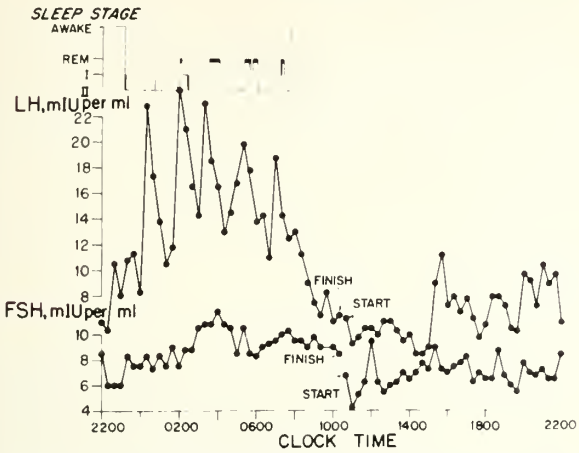


Figure 14.—Plasma luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations sampled every 20 minutes for 24 hours in a normal 13-year-old pubertal girl. A sleep histogram is shown above the period of nocturnal sleep. Sleep stages are awake and REM (rapid eye movement); stages 1 through 4 are indicated by the depth of line graph. (Reproduced by permission from Boyar et al.[17])

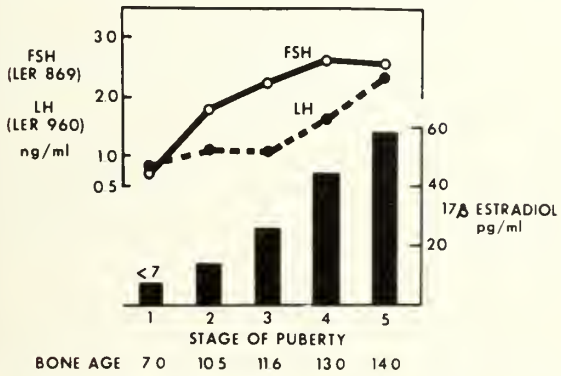


Figure 15.—Mean plasma estradiol, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations in prepubertal and pubertal girls by stage of maturation. (Reproduced by permission from Grumbach.[26])

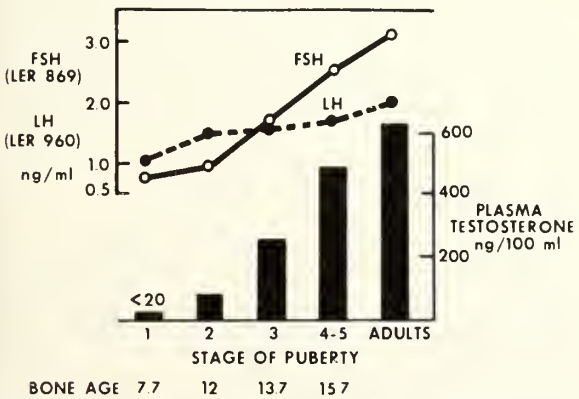


Figure 16.—Mean plasma testosterone and gonadotropin in normal boys by stage of maturation. (Reproduced by permission from Grumbach.[26])

and FSH.[13,14] Thus the system in primates is dampened or inhibited in this preadolescent period. It also may be shown that this inhibition is not related to gonadal function, for not only does castration fail to produce large rises in FSH and LH, but, in agonadal children studied at the *usual age* of puberty, gonadotropins rise steadily to castrate adult concentrations. These changes are shown in Figures 12 and 13. Since infusion of the 10-amino acid hypothalamic peptide gonadotropin releasing hormone (GnRH) produces a rise in blood LH and FSH in prepubertal children, this inhibition appears to act by way of decreased GnRH secretion or its effects.[15] Interestingly, near birth in humans, agonadal children have LH and FSH levels as high as castrate adults. This indicates the inhibition of the preadolescent system is developed during early infancy.

As this poorly understood inhibitory system is being disengaged in humans, the augmentation in gonadotropin secretion is first observed during sleep, rather than during waking hours. Figure 14 shows these data. Boyar and co-workers[16,17] have shown that once sexual maturation has been initiated, sleep induces a rise in blood LH (and possibly FSH). During this period, the awake stage is associated with low LH and FSH values. As maturation is completed over several years, daytime or awake LH and FSH levels rise to equal those previously observed during sleep until 24-hour values are relatively constant.[11]

In humans, after the inhibitory controls of the preadolescent period are removed, FSH and LH concentrations rise 100 percent to 300 percent in concert with blood testosterone or estradiol. Figures 15 and 16 show these data for boys and girls, respectively.

Also it appears likely that, as in rodents, sensitivity to LH changes during the pubertal years. Data are limited but Sizonenko and associates[18] have used human chorionic gonadotropin (HCG), an LH-like hormone, to stimulate Leydig cell secretion of testosterone in prepubertal boys. The increment in blood testosterone correlated well with basal FSH, but not with basal LH concentrations (Figure 17).

Lastly, whether changes in negative feedback sensitivity occur in any animals is presently debatable. The studies of Kallas[19] and Byrnes[20] have been evaluated earlier[2] and were done before LH and FSH assays. Furthermore, in these often cited studies, direct comparisons of feedback sen-

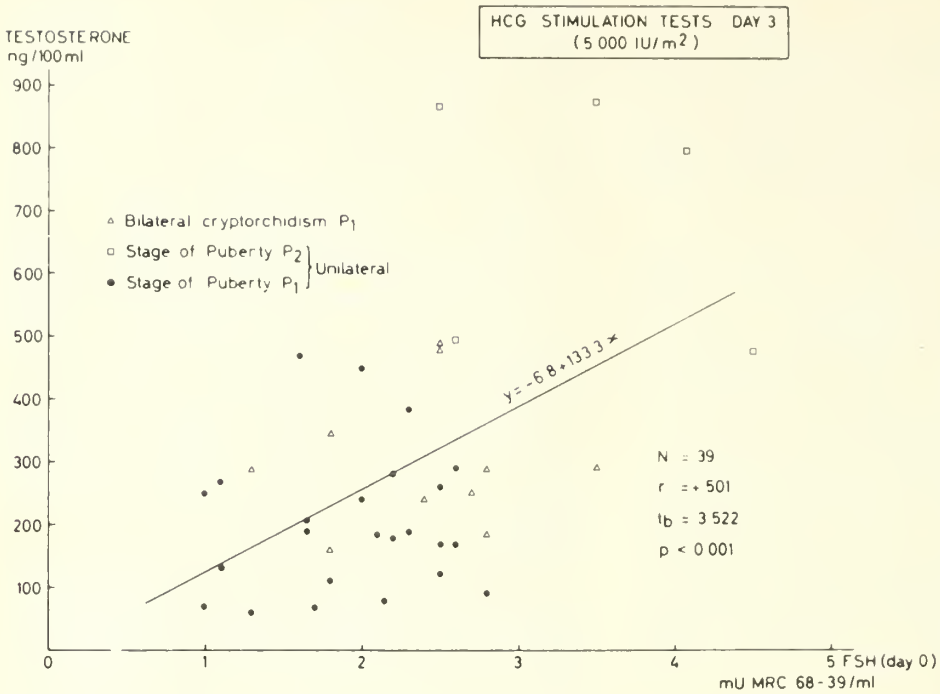


Figure 17.—Plasma testosterone concentrations obtained on day 3 after human chorionic gonadotropin (HCG) administration and plasma levels of follicle-stimulating hormone (FSH) on day 0 in 39 cases of cryptorchidism in stages P_1 and P_2 puberty. (Reproduced by permission from Sizonenko.[18])

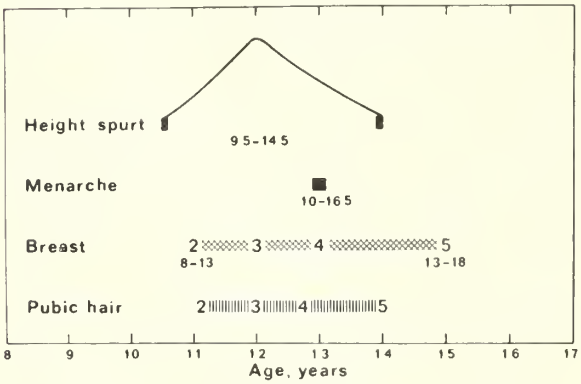


Figure 18.—Schematic sequence of events at puberty. An average girl is represented. The range of ages within which each event charted may begin and end is given by figures placed directly below its start and finish. (Reproduced by permission from Tanner.[23])

sitivity between adult and prepubertal animals were not made. We were unable to correlate negative feedback sensitivity to sexual maturation in animals.[2] Grumbach and co-workers[21] and Kulin and associates[22] have studied sensitivity in children. The data are few, but show a possible threefold to fivefold difference in negative feedback sensitivity between early stages of puberty and sexual maturity.

In summary, sexual maturation in humans appears to involve both gonadal and hypothalamic-pituitary factors:

- A preadolescent inhibitory or dampening of the hypothalamic-pituitary-gonadal control system is present. This inhibition is initiated at 6 to 36 months of age and is removed at 8 to 10 years of age. This system is poorly understood but probably is mediated by decreased GnRH secretion.
- The prepubertal gonad is less responsive to LH than the mature gonad. The prepubertal gonad is as responsive to FSH as the adult gonad. FSH induces new LH receptor formation and induces increased gonadal response to LH.
- Once puberty has been initiated, sleep induces LH and FSH secretion.
- Once the process of sexual maturation has been initiated threefold to fivefold changes in negative feedback sensitivity occur explaining the rising gonadotropin concentrations during pubertal stages 2 to 5.

The Physical Changes of Puberty

Figures 18 and 19 show the age of onset, interrelations and duration of secondary sex characteristics, development, growth spurt and pubertal stage development in an average girl and boy, respectively, from data of Tanner.[1] The immediate cause of these changes is, of course, androgenic steroids derived mainly from the testes in boys and estrogenic steroids from the ovaries in

girls. Additionally, in girls, adrenal-derived androgens are important in pubic and axillary hair development. The age that any given pubertal stage occurs, or the age of menarche, is more closely correlated with skeletal age than with

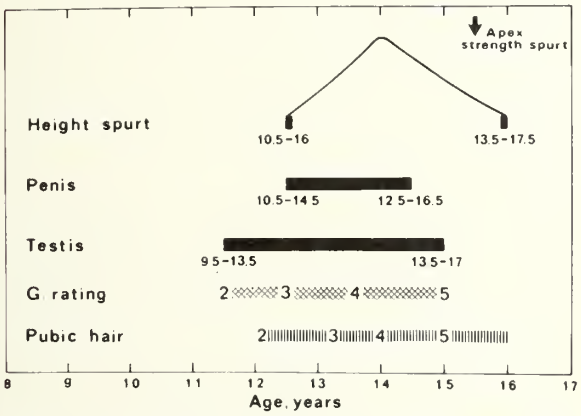


Figure 19.—Schematic sequence of events at puberty. An average boy is represented. The range of ages within which each event charted may begin and end is given by the figures placed directly below its start and finish. G indicates genital. (Reproduced by permission from Tanner.[23])

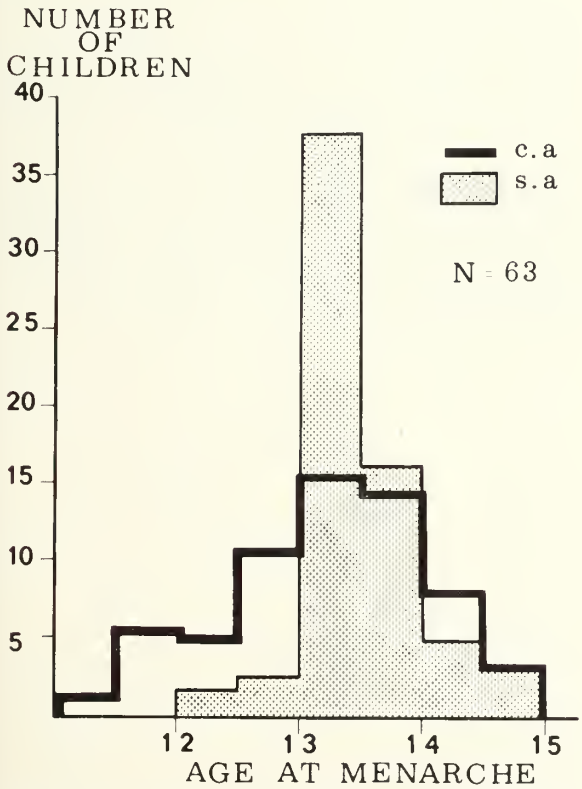


Figure 20.—Variation of chronological (c.a.) and skeletal (s.a.) ages at menarche. (Reproduced by permission from Marshall.[29])

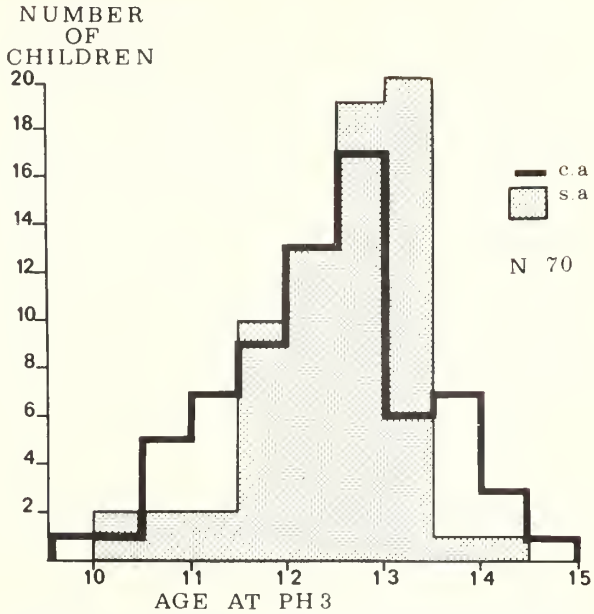


Figure 21.—Variation of chronological (c.a.) and skeletal (s.a.) ages at pubic hair (PH) stage. (Reproduced by permission from Marshall.[29])

chronological age. For example, Figure 20 shows the distribution of age of menarche in girls and Figure 21 shows the age of pubertal stage 3 in boys plotted against chronological and skeletal ages from data of Marshall.[23] In addition to these changes in sex characteristics, sexual maturation is, of course, associated with many other body changes generally relatable to sex steroid actions. These include changes in growth velocity, emotional and mental process changes, changes in body fat and muscle strength development, changes in voice, skin and body hair. We will not discuss these in any detail due to space limitations. One example may be useful: the growth velocity. Figure 22 shows individual velocity curves for boys and girls from data of Tanner.[23] Figure 23 shows data from five boys plotted against chronological age and against years before and after peak velocity, independent of chronological age. Note the homogeneity in velocity curves expressed in relation to peak velocity.

Adrenarche

Independent of maturation of gonadal function, adrenal androgen secretion increases during prepubertal and pubertal years. It was initially felt that adrenarche occurred at the same time as gonadal maturation. This belief was based on measurements of 24-hour urinary 17-ketosteroid excretion using relatively insensitive methods.

Changing adrenal androgen secretion is not associated with changing cortisol secretion and presumably a nonadrenocorticotropic hormone (non-ACTH) pituitary factor modulates androgen secretion. However, its nature remains unknown. Parker and Odell[24] have shown it is not likely to be LH, FSH, prolactin or growth hormone. However, prolactin receptors have been identified in the adrenal gland[25] and several workers have postulated a role for prolactin in modulating adrenal androgen secretion. Figure 24 shows changes in androstenedione and dehydroepiandrosterone (DHEA) with chronological age. Note that these androgens, chiefly derived from the adrenal gland, begin to rise in blood several years before pubertal changes and rise steadily throughout preadolescent and pubertal years.

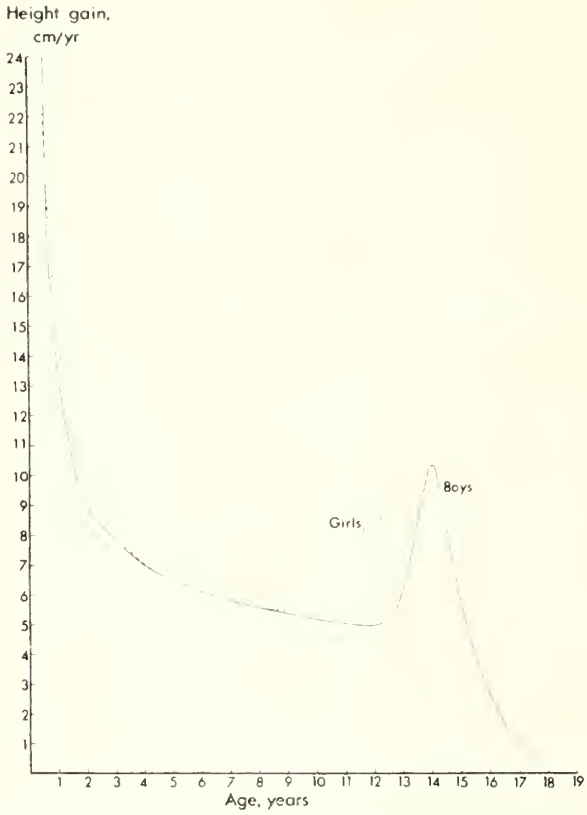


Figure 22.—"Typical-individual" velocity curves for supine length or height in boys and girls. (Reproduced by permission from Tanner.[21])

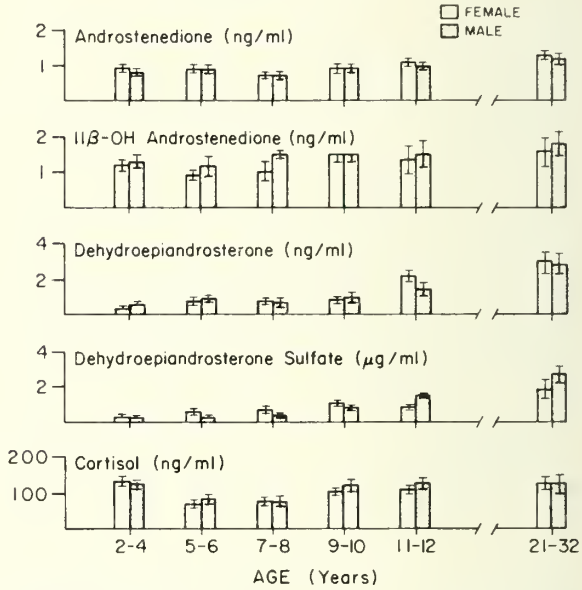


Figure 24.—Steroid hormones: concentrations of androstenedione, 11β-androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate and cortisol with increasing age. Data presented as mean±SEM. (Reproduced by permission from Parker et al.[28])

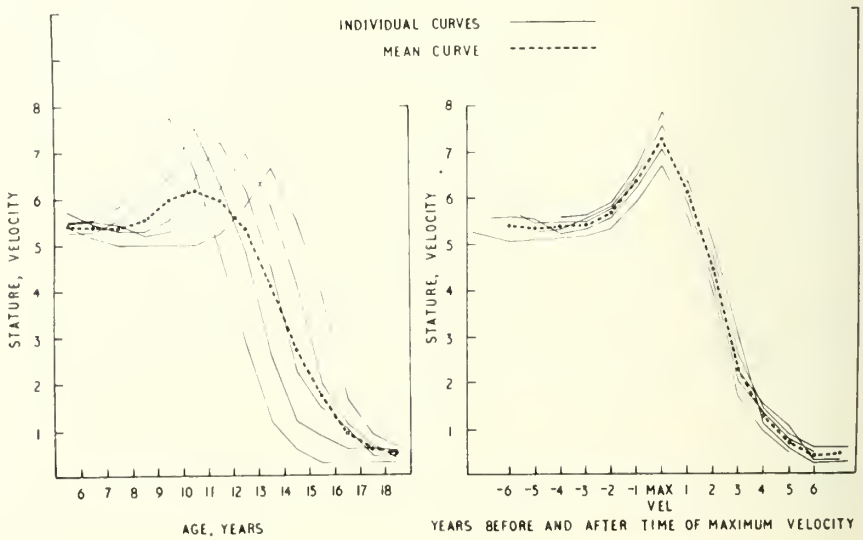


Figure 23.—Height velocity curves of five boys, plotted against chronological age **(left)** and age at peak height velocity **(right).** (Reproduced by permission from Tanner.[1])

Primary Amenorrhea

DANIEL D. FEDERMAN, MD*

Introduction

PRIMARY AMENORRHEA, or the absence of any menstrual function, is the normal state for prepubertal girls and does not become a disease or symptom until the expected date of puberty. The secular trend in the date of menarche now places the median age at 13. Of normal girls, 95 percent will have had their first period by age 15; the absence of menstruation beyond that date can be defined as primary amenorrhea, although it may not turn out to herald significant disease. Because breast development ordinarily antedates menarche by approximately two years, the absence of progressive breast enlargement by age 13 can similarly be taken as a stimulus to evaluation, if not as definitive evidence of abnormality.

It should be emphasized that most suspected abnormalities of pubertal development turn out to be variations of the normal, with excellent prognosis, rather than disease. With this probability in mind, a conservative and expectant approach to diagnosis and therapy is usually appropriate, but the clinician should be aware of screening tests that provide either strong reassurance or an early alert to true disease.

Normal Physiology Recapitulated

Dr. Odell has outlined the normal physiology of menstruation. Although the event that triggers puberty is unknown, normal menses ultimately require the presence of normal hypothalamic, pituitary and ovarian function.

Required Functions

The hypothalamus must secrete gonadotropin releasing hormone (GnRH) both at a basal level and, when exposed to high estrogen levels, in an abrupt surge. The pituitary must be able to produce both gonadotropins: FSH initiates follicular development and estrogen synthesis and, when appropriate follicular development has occurred, LH triggers ovulation.

The ovary secretes estrogen in progressively increasing amounts over an approximately 12-day period; when the plasma estradiol reaches a critical level, positive feedback stimulates both an increase in GnRH output and an enhanced pituitary response to GnRH.[30] The result is a sudden surge of both FSH and LH, leading to ovulation. Following ovulation, the corpus luteum secretes large amounts of progesterone. Finally, if pregnancy does not occur, both estrogen and progesterone levels fall, and several days later menstrual flow begins.

The uterus must be able to respond to both hormones, and, finally, there must be a patent cervix and introitus in order for the menstrual blood to be shed.

Absence of an Excess of Three Classes of Hormones

Three types of hormones, when secreted in excess, are capable of interfering with an otherwise intact hypothalamic-pituitary-ovarian-uterine system. The three potentially interfering hormones are cortisol, prolactin and androgens. The evaluation of patients with delayed menarche must thus be addressed both to the *presence* of hypothalamic, pituitary and ovarian competence and to the *absence* of those hormones capable of intruding on the system.

Central Causes of Primary Amenorrhea

Central causes of primary amenorrhea refer to hypothalamic and pituitary disorders that cause either absence of the releasing hormone or failure of the pituitary gland to respond to it.[31] The clinical manifestations of these defects are due to absence of both gonadotropins, with resultant deficiency in both breast development and menstrual function.

Absence of Hypothalamic Releasing Hormone

- *Physiologically delayed puberty*

The onset of puberty appears to be genetically determined. Therefore, particularly in a child who is growing slowly, the story that the mother or sisters had a later onset of puberty is strong reassurance that the patient will ultimately develop periods of her own. Nevertheless, when a child of 14 or 15 has not yet undergone breast development, a plasma FSH determination should be obtained. Since concentrations of FSH (and LH) fluctuate rhythmically each 10 to 20 minutes, the average of three specimens is more precise than a single determination. A low or normal value is consistent with later normal development. If

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the FSH is elevated, it provides evidence of ovarian failure and should stimulate a further workup.

- *Nutritional causation*

There is considerable evidence that the onset of puberty is tied to the attainment of a critical body weight.[32] Children who are short and growing slowly but steadily often have a late menarche. Children who are pathologically short, particularly when they have been nutritionally deprived because of emotional factors, often have a late puberty. In addition, disorders such as regional enteritis are often clinically subtle in teenage girls and may also cause amenorrhea. In the presence or normal or low LH and FSH levels and primary amenorrhea, this category of causes should be carefully considered. Professional athletes or marathon runners also have a high incidence of amenorrhea probably related to alterations in body fat:muscle ratios, factors which may be implicated in this nutritional category.

- *Deficiency of gonadotropin releasing hormone*

Although more common in males, idiopathic absence of GnRH occurs in females as well. It is occasionally associated with absence (anosmia) or impairment (hyposmia) of the ability to smell. When either of these defects is found in association with pubertal delay, the diagnosis of the Kallman syndrome is established. The serum gonadotropin will be found to be low, and replacement therapy is appropriate.

In a patient with a normal sense of smell, it is extraordinarily difficult to make the differential diagnosis between idiopathic gonadotropin releasing hormone deficiency and physiological delay of puberty. In a normal prepubertal girl, GnRH administration increases FSH in relation to LH to a much greater extent then following puberty or in most patients with GnRH deficiency. Consequently, this GnRH test may help to distinguish GnRH deficiency from delayed puberty. In addition, the administration of GnRH ought to distinguish patients who lack GnRH from those with pituitary disease who are simply unable to respond to GnRH; unfortunately, many reports have documented an overlap in results of such tests.[33] In other patients, however, daily administration of GnRH awakens a gonadotropin response by the pituitary that is initially sluggish. There is thus considerable ambiguity in results. Recent studies from various laboratories have suggested that the hypothalamic defect is more complex than was originally supposed and that various abnormalities of other releasing hormones and tropic hormone responses may be involved. Suprasellar tumors (such as craniopharyngiomas, teratomas) may also produce GnRH deficiency and amenorrhea.

Pituitary Deficiency

The inability to synthesize gonadotropin despite adequate GnRH stimulation would, of course, also be a cause of primary amenorrhea. As an isolated biosynthetic defect, this failure appears to be less common than GnRH deficiency. As a component of hypopituitarism, however, gonadotropin deficiency occurs early and, therefore, children with developing pituitary insufficiency may have a defect in gonadotropin production, while thyroid and adrenal function remain normal. Ordinarily, however, growth hormone is impaired approximately as early as is gonadotropin; therefore, children who have primary amenorrhea because of pituitary deficiency usually show a defect in growth. It is exactly in this context that plotting a child's growth pattern is the most valuable (and simultaneously the cheapest) laboratory test available. If the child maintains a growth pattern consistent with the rate of growth shown in earlier years, strong reassurance against acquired pituitary growth hormone deficiency can be inferred.

The pituitary lesions that may be responsible for gonadotropin deficiency include tumor, granuloma and infarction. All are relatively uncommon, of course, but the commonest one, pituitary tumor, can often be shown by tomograms of the sella; one is looking in particular for asymmetric contours of a normal-size sella or enlargement of the sella. Suprasellar calcification may indicate the presence of a craniopharyngioma which can cause GnRH deficiency or directly involve the pituitary (or both). Measurement of the serum prolactin will also alert the physician to the approximately 30 percent to 50 percent of pituitary tumors that were formerly thought to be without function but are known to be prolactin-secreting.

Physical examination also helps in the elucidation of gonadotropin deficiency. In a child who was formerly normal, had breast development on time but then failed to menstruate because of pituitary deficiency secondary to a tumor, a growth defect may be shown at approximately the time of expected menstruation. In contrast, in a child who is short and unable to secrete estrogen be-

cause of an ovarian defect, growth impairment would have been shown much earlier.

It cannot be emphasized too often that plasma or serum gonadotropin measurements are the best way to establish the site of the abnormality. If the gonadotropin levels are low or normal, a central defect can be presumed; if an x-ray study of the skull shows no abnormalities, one can wait, although temporary estrogen therapy can be considered for psychological reasons. If the gonadotropin values are high, the defect is in the ovary.

Ovarian Defects

Ovarian inability to produce estrogen and progesterone despite adequate gonadotropin stimulation is a well-established source of primary amenorrhea. Three principal classes of defect can be delineated: chromosomal errors in gonadal differentiation, primary biosynthetic defects in estrogen manufacture and excess androgen production.

Defective Ovarian Differentiation

The classic ovarian defect is the Turner syndrome, or ovarian agenesis.[34] In the complete syndrome, a 45,X karyotype is associated with a variety of congenital anomalies, growth retardation evident by about the third or fourth year of life, and complete lack of estrogen. These patients are usually promptly recognized on physical examination, and the suspected diagnosis can be confirmed by a chromatin-negative buccal smear and elevated plasma FSH.

The variants of gonadal dysgenesis provide somewhat greater difficulty with diagnosis and, therefore, are worth individual mention.[35]

- *Mosaic gonadal dysgenesis*

These patients have a mixture of abnormal and normal cells (45,X/46,XY). For reasons that are intuitively likely but not yet quantitatively understood, these patients have partial manifestation of the Turner syndrome; any combination of anomalies, short stature and menstrual difficulty may be seen. If the anomalies are trivial and the growth defect minimal, primary amenorrhea of this origin can be difficult to recognize, but the elevation of the FSH should provide an alert.

- *Pure gonadal dysgenesis*

Occasional patients with either a 46,XY or a 46,XX karyotype have the same gonadal defect as patients with the Turner syndrome but have neither the anomalies nor the growth retardation. In the absence of short stature in a patient, a clinician may have difficulty recognizing the diagnosis. Clues are the absence of breast development and a normal but small uterus. In those who are 46,XY there will be a chromatin-negative buccal smear, and in both groups of patients gonadotropin will be elevated.

- *Mixed (or asymmetric) gonadal dysgenesis*

In mixed gonadal dysgenesis, the patient has a streak gonad plus a testis. Most patients come to attention as newborns because of ambiguity of the external genitalia. If the ambiguity is overlooked, they are usually recognized in early puberty because of virilization. But they may escape diagnosis until absence of breast development and primary amenorrhea are recognized. The karyotypic defect varies, but most often it is a mosaic pattern, that is 45,X/46,XY. The characteristic laboratory findings are a chromatin-negative buccal smear, an elevated plasma testosterone and high gonadotropin.

Difficulty With Estrogen Biosynthesis

Several defects in steroid biosynthesis may result in a decreased synthesis of estrogens. These include:

- *The 17-hydroxylase deficiency*

A deficiency of the 17-hydroxylase enzyme in the ovaries and adrenals produces a decrease in both estrogen and cortisol synthesis. These patients lack estrogen effects, are usually hypertensive, have low blood cortisol, and elevated progesterone and corticosterone concentrations.

- *The 17-ketosteroid reductase deficiency*

The 17-ketosteroid reductase deficiency results in an inability or decreased ability to convert androstenedione to testosterone and estrone to estradiol. In an XY male, this results in a phenotypic female with absent uterus, amenorrhea and hirsutism. The low testosterone concentrations *in utero* result in pseudohermaphroditism, but the elevated androstenedione produces hirsutism.

- *Defects in early steps of steroidogenesis*

Deficiencies of the cholesterol desmolase or 3βol dehydrogenase enzymes usually produce death early in infancy unless diagnosed and treated. They have not yet been reported to

present in later life as amenorrhea, but this would be anticipated since sex steroid production would be deficient.

Excess Androgen Production

Excess androgen production as a cause of primary amenorrhea is seen primarily with variants of the Stein-Leventhal or polycystic ovary syndrome (PCO). Although usually noted for secondary amenorrhea, the PCO syndrome can cause primary amenorrhea. Patients have breast development, usually have some degree of hirsutism and may be quite muscular. FSH is normal, but LH is usually high normal, though acyclic. Endocrine findings are extremely variable in these patients, but there is usually some elevation of plasma androgens and estrone.

Absence of Uterus

Absence of the uterus, with intact female endocrine function, produces a unique history and physical examination findings that result in the diagnosis of the Rokitansky syndrome. At birth, the patient has a normal newborn appearance, although in some cases the vagina is also absent. Growth and development, with timely breast enlargement, normal pubic hair, and normal estrogen production and serum FSH contribute to the picture of a normal puberty. Yet, for no known reason, the uterus is missing. On examination the patient is shown to have a normal XX karyotype, and an ultrasound examination of the pelvic organs or laparoscopy may be needed to confirm the absence of the uterus.

Absence of the uterus may be associated with a radically different disorder: male pseudohermaphroditism. The classic example is testicular feminization or androgen resistance syndromes. In these, the patients are genetic males who lack the cell receptor for testosterone. They have plasma testosterone concentrations which are normal for a male, but are biochemically unable to respond to this testosterone. In the fetus the testes secrete müllerian-duct inhibiting hormone and thus suppression of müllerian structures occurs. Therefore, these patients have no uterus and a shallow blind vagina; lacking effective testosterone, however, they do not differentiate male internal or external genitalia. They often come to pediatric attention because of an inguinal hernia caused by

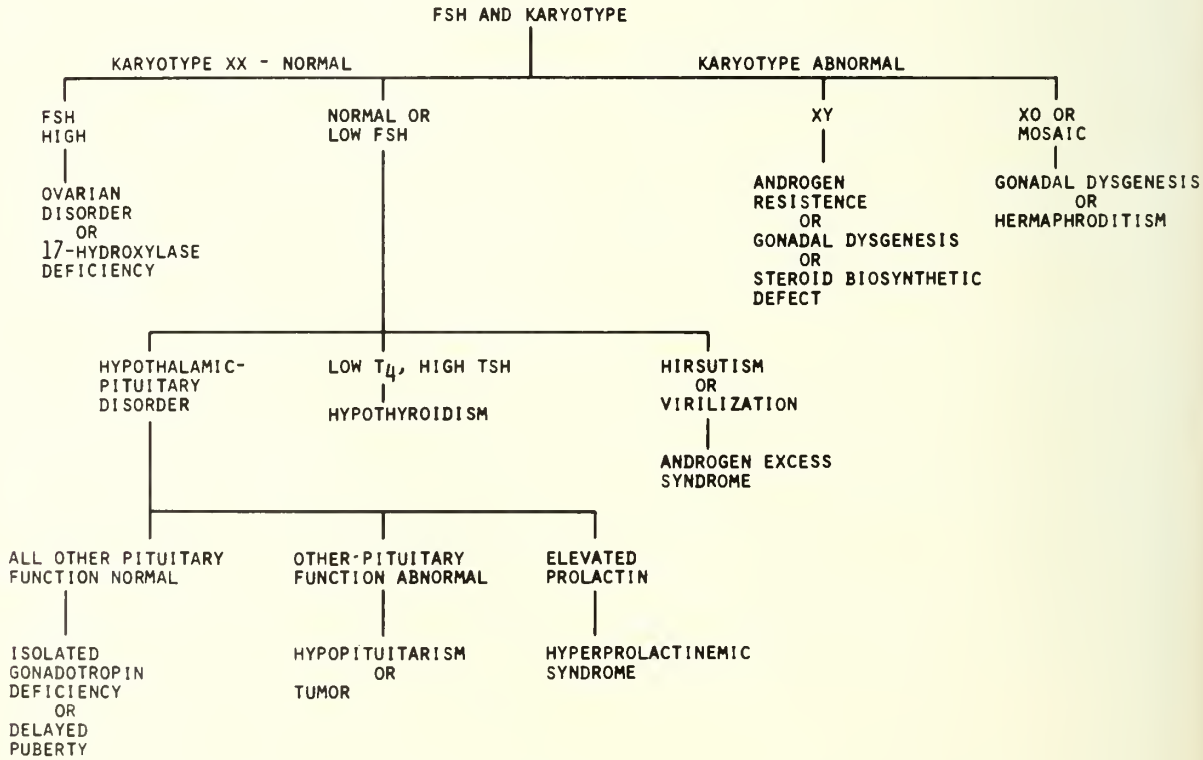

Figure 25.—Outline for the diagnosis of patients with primary amenorrhea.

the attempted descent of the testis. Otherwise, they develop in a normal female pattern, having the breast development of normal female puberty, but lacking a uterus they cannot have periods. The findings on physical examination in complete androgen resistance are a critical clue to this diagnosis: the patient is normal in height, has breast development, but has neither pubic or axillary hair nor a palpable uterus. The laboratory findings show elevated plasma testosterone (for a female) and estradiol but only minimally elevated FSH. The critical laboratory finding is an XY normal male karyotype.

Milder variants of this disease with partial androgen resistance accompanied by some degree of genital ambiguity or pubertal virilization, are also seen. Paradoxically, although milder, they are less difficult to diagnose because the virilization in a patient with primary amenorrhea suggests the diagnosis. The 17 ketosteroid reductase enzyme deficiency previously mentioned has often been mistaken for incomplete androgen resistance.

Interfering Hormones

Three types of hormones may interfere with the onset of normal menstrual function. Cortisol in the context of adrenal hyperfunction and the Cushing syndrome is well known. Although the clinical manifestations may not be striking, other features of cortisol excess will usually be evident on physical examination. In other words, primary amenorrhea is not likely to be the only feature of the Cushing syndrome. For confirmation, the usual tests for the Cushing syndrome should be undertaken; in the simplest screening test, 1 mg of dexamethasone is given at midnight and a plasma cortisol determination is done the following morning. Cortisol values less than 5 μg per dl eliminate the Cushing syndrome from consideration.

Prolactin elevation may be a cause of primary amenorrhea. Although much more common as a cause of secondary amenorrhea, prolactin elevation has also been reported with pituitary tumors as a cause of primary amenorrhea.

Finally, androgen excess can also prevent the onset of normal menstrual function. Adrenal androgens may be hypersecreted either by adrenal tumors, which can develop at any time, or in the syndrome of congenital adrenal hyperplasia. Most patients with congenital adrenal hyperplasia come to attention as newborns because of genital ambiguity. Very occasionally, the onset of the defect is manifest at puberty; such patients have absent or minimal breast development, excessive hair growth and primary amenorrhea. They are chromatin-positive, and their androgen levels are high.

Workup and Evaluation

The workup appropriate to investigate primary amenorrhea has been implied in the preceding sections. Although many laboratory tests can be helpful, the history and physical examination should provide the clue to the diagnosis most of the time, making one or two confirmatory laboratory tests adequate.

The history should emphasize the family pattern of menstrual onset, previous growth and development, recent changes in general health and the onset of breast development. Physical examination should focus on height, degree of muscularity, the anomalies of the Turner syndrome, hirsutism or other signs of virilization, presence or absence of breast enlargement, and presence or absence of a uterus.

If there is no evidence of estrogen secretion, plasma FSH should be quantified to orient the diagnosis toward a central or ovarian cause. A karyotype is indicated if the gonadotropin value is high or if there is no uterus palpable. Based on the FSH and karyotype results the patients may be placed into one of the diagnostic categories outlined in Figure 25. Measurements of other pituitary hormones, thyroid hormones, androgens or steroid hormone precursors should then be made if indicated.

REFERENCES

1. Tanner JM: Growth at Adolescence. Oxford, Blackwell Science Publications, 1962

2. Odell WD, Swerdloff RS: Etiologies of sexual maturation: A model system based on the sexually maturing rat. Rec Prog Horm Res 32:245-288, 1976

3. McCann SM, Ojeda S, Negro-Vilar A: Sex steroids, pituitary and hypothalamic hormones during puberty in experimental animals, *In* Grumbach MM, Grave GD, Mayer FE (Eds): The Control of Onset of Puberty. New York City, John Wiley & Sons Inc, 1974, p 1

4. Selmanoff MK, Goldman BD, Ginsburg BE: Developmental changes in serum luteinizing hormone, follicle stimulating hormone and androgen levels in males of two inbred mouse strains. Endocrinology 100:122-127, Jan 1977

5. Odell WD, Hescox MA, Kiddy CA: Studies of hypothalamic-pituitary-gonadal interrelations in prepubertal cattle, *In* Butt WR, Crooke AC, Ryle M (Eds): Gonadotropins and Ovarian Development, Edinburgh, Livingston, 1970, pp 371-385

6. Gonzalez-Padilla E, Wiltbank JN, Niswender GD: Puberty in beef heifers—The interrelationship between pituitary, hypothalamic and ovarian hormones. J Anim Sci 40:1019-1104, Jun 1975

7. Karg H, Gimenez T, Hartl M, et al: Testosterone luteinizing hormone (LH) and follicle stimulating hormone (FSH) in peripheral plasma of bulls: Levels from birth through puberty and short term variations. Zentralblatt Vet Med A 23:793-803, Dec 1976

8. Elsaesser F, Pomerantz KK, Elendorff F, et al: Plasma LH testosterone and DHT in the pig from birth to sexual maturity. Acta Endrocrinol (Copen) 173(Suppl):148, 1973

9. Swerdloff RS, Jacobs HS, Odell WD: Hypothalamic-pituitary gonadal interrelationships in the rat during sexual maturation, *In* Saxena BB, Beling CG, Gandy HM (Eds): Gonadotropins. New York City, John Wiley & Sons, Inc, 1972, pp 546-561

10. Swerdloff RS, Walsh P, Jacobs HS, et al: Serum LH and FSH during sexual maturation in the male rat—Effect of castration and cryptorchidism. Endocrinology 88:120-128, Jan 1970

11. Odell WD, Swerdloff RS, Jacobs JD, et al: FSH induction of sensitivity to LH: One cause of sexual maturation in the male rat. Endocrinology 92:160-165, Jan 1973

12. Odell WD, Swedloff RS, Bain J, et al: The effect of sexual maturation on testicular response to LH stimuation of testosterone secretion in the intact rat. Endocrinology 95:1380-1384, Nov 1974

13. Conte FA, Grumbach MM, Kaplan SL: A diphasic pattern of gonadotropin secretion in patients with the syndrome of gonadal dysgenesis. J Clin Endocrinol Metab 40:670-675, Apr 1975

14. Winter JS, Faiman C: Serum gonadotropin in agonadal children and adults. J Clin Endocrinol Metab 35:561-564, Oct 1972

15. Job JC, Garnier PE, Chaussain JL, et al: Effect of synthetic luteinizing hormone-releasing hormone (LR-RH) on serum gonadotropins (LH and FSH) in normal children and adults. Revue Europeene d'Etudes Cliniques et Biologiques 17:411-414, Apr 1972

16. Boyar R, Finkelstein J, Roffwarg H, et al: Synchronization of augmented luteinizing hormone secretion with sleep during puberty. N Engl J Med 287:582-586, Sep 1972

17. Boyar RM, Finkelstein JW, David R, et al: Twenty-four hour patterns of plasma luteinizing hormone and follicle stimulating hormone in sexual precocity. N Engl J Med 289:282-286, Aug 1973

18. Sizonenko P, Cuendet A, Paunier L: FSH—I. Evidence for its mediating role on testosterone secretion in cryptorchidism. J Clin Endocrinol Metab 37:68-73, Jul 1973

19. Kallas H: Puberté précoce pariparabiose. C R Soc Biol (Paris) 100:979, Apr 1929

20. Byrnes WW, Meyer RK: The inhibition of gonadotrophic hormone secretion by physiological doses of estrogen. Endocrinology 48:133-136, Feb 1951

21. Grumbach MM, Roth JC, Kaplan SL, et al: Hypothalamic-pituitary regulation of puberty: Evidence and concepts derived from clinical research, *In* Grumbach MM, Grave GD, Mayer FE (Eds): The Control of the Onset of Puberty. New York City, John Wiley & Sons Inc, 1974, p 115

22. Kulin HE, Reiter OE: Gonadotropin suppression by low dose estrogen in men: Evidence for differential effects upon FSH and LH. J Clin Endocrinol Metab 35:836-839, Dec 1972

23. Tanner JM: Sequence and tempo in the somatic changes in puberty, *In* Grumbach MM, Grave GD, Mayer FE (Eds): The Control of the Onset of Puberty. New York City, John Wiley & Sons Inc, 1974, p 448

24. Parker LN, Odell WD: Evidence for existence of cortical androgen-stimulating hormone. Am J Physiol 236:E616-E620, Jun 1979

25. Parker LN, Chang S, Odell WD: Adrenal androgens in patients with chronic marked elevation of prolactin. Clin Endocrinol 8:1-6, Jan 1978

26. Grumbach MM: Onset of puberty, *In* Berenberg SR (Ed): Puberty—Biologic and Psychosocial Components, Leiden, Netherlands, H.E. Stenfert-Kroese BV, 1975, pp 1-21

27. Tanner JM, Whitehouse RH, Takaishi M: Standards from birth to maturity for height, weight, height velocity, weight velocity. British children—Part I. Arch Dis Child 41:454-471, Oct 1966

28. Parker LN, Sack J, Fisher DA, et al: The adrenarche: Prolactin, gonadotropins, adrenal adrogens, and cortisol. J Clin Endocrinol Metab 46:396-401, Mar 1978

29. Marshall WA: Interrelationships of skeletal maturation, sexual development and somatic growth in man. Ann Human Biol 1:29-40, Jan-Mar 1974

30. Yen SSC: The human menstrual cycle (integrative function of the hypothalamic-pituitary-ovarian-endometrial axis). *In* Yen SSC, Jaffe RB (Eds): Reproductive Endocrinology. Philadelphia, WB Saunders Co, 1978, chap 7

31. Ross GT, Vande Weile RL: The Ovaries, *In* Williams RH (Ed): Textbook of Endocrinology. Philadelphia, WB Saunders Co, 1974, chap 7

32. Frisch RE, McArthur JW: Menstrual cycles: Fatness as a determinant of minimum weight for height necessary for their maintenance or onset. Science 185:949-951, Sep 1974

33. Yoshimoto Y, Moridera K, Imura H: Restoration of normal pituitary gonadotropin reserve by administration of luteinizing-hormone-releasing hormone in patients with hypogonadotropic hypogonadism. N Engl J Med 292:242-245, Jan 1975

34. Neu RL, Gardner LI: Abnormalities of sex chromosomes, *In* Gardner LI (Ed): Endocrine and Genetic Diseases of Childhood and Adolescence, 2nd Ed. Philadelphia, WB Saunders Co, 1975, pp 793-814

35. Federman DD: Disorder of gonadal development: Mixed gonadal dysgenesis—Dysgenetic male pseudohermaphroditism: Agonadism, *In* Federman DD (Ed): A Genetic and Endocrine Approach to Differential Diagnosis. Philadelphia, WB Saunders Co, 1967, chap 6

36. Zurbrugg RP: Congenital adrenal hyperplasia, *In* Gardner LI (Ed): Endocrine and Genetic Diseases of Childhood and Adolescence, 2nd Ed. Philadelphia, WB Saunders Co 1975, pp 476-500

Refer to: Scharschmidt B: Cimetidine—Medical Staff Conference, University of California, San Francisco. West J Med 131: 417-425, Nov 1979

Cimetidine

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, CA 94143.

DR. SMITH:* *This morning we shall consider a recently marketed pharmacologic agent with rather widespread efficacy in gastrointestinal disease. Dr. Bruce Scharschmidt of the division of gastroenterology will lead the discussion of cimetidine.*

DR. SCHARSCHMIDT:† Few drugs have had as great an impact on the medical community as cimetidine. The most obvious reason for this is the very large patient population that might potentially benefit from its use. For example, peptic ulcer develops in as many as 10 percent of all adults at some time, and, each year in the United States alone, there are more than 400,000 hospital admissions for peptic ulcer and 4 million hospital days devoted to peptic ulcer treatment. Since an even greater number of people have acid indigestion, the demand for this drug from a well-read lay public has been enormous. In fact, within 14 months of the drug's release, nearly 1 percent of the United States population had received cimetidine. Given this widespread use of a relatively new drug, it is worthwhile reviewing the information available regarding its actions, efficacy and safety. This morning I shall describe briefly the fascinating history of how this drug was developed and will review current information regarding its pharmacology, clinical efficacy, toxicity and cost. I shall then try to summarize current perspective on where this drug belongs in our armamentarium.

Development of Cimetidine as a Histamine H_2-Receptor Antagonist

The principal pharmacologic effects of histamine itself were described in a classic series of papers written between 1910 and 1919 by Dale and Laidlaw. Ironically, the only histamine effect of importance which they failed to appreciate was that on gastric secretion. Between 1937 and 1946 a series of antihistamines were developed, of which mepyramine, the prototype, is shown in Figure 1. As a group, these drugs are now known as H_1 receptor antagonists or more simply as antihistamines. They have a positively charged ammonium group at the end of a side chain attached to an aryl ring instead of an imidazole ring

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†Bruce Scharschmidt MD, Assistant Professor of Medicine.

as in histamine. These drugs block histamine-induced contraction of ileal, bronchial and uterine smooth muscle in certain species. However, they only partially block the profound vasodilatation induced by histamine and they have no effect on gastric secretion.[1]

Fifteen years ago, Smith Kline and French Laboratories initiated a research program to develop a compound which would block the remaining effects of histamine.[2] Burimamide, the first H_2 blocker, was produced in 1972, and metiamide and cimetidine followed in rapid succession. These drugs have an imidazole ring, as does histamine, but they have a much less basic and longer side chain (Figure 1). It is noteworthy that cimetidine has a cyanoguanidine group, whereas metiamide, its forerunner, had a thiourea group. This may explain why cimetidine use has not been associated with the same severe agranulocytosis occasionally produced by metiamide.

The H_2 receptors block experimental effects of histamine on guinea pig heart muscle and rat uterus.[1,2] We are still learning of their effects in humans. If appears that they partially block the vasodilatory effect of histamine and they profoundly inhibit gastric acid secretion. In fact, they inhibit not only the stimulatory effect of histamine on acid secretion, but they also block the effect of all known secretagogues including gastrin and acetylcholine.

Mechanism of Action

The ability of cimetidine to inhibit acid secretion stimulated by acetylcholine and gastrin, as well as histamine, has led to two general theories regarding its mechanism of action.[3] These are illustrated simplistically in Figure 2. One postulate is that gastrin and acetylcholine act by increasing histamine production or release in gastric mucosa, which in turn stimulates acid secretion. Cimetidine, by blocking the final common mediator, blocks all secretagogues. A second explanation holds that all three secretagogues, by an as yet unidentified mechanism, are mutual potentiators of acid secretion. That is, the effect of any two secretagogues together is greater than the sum of their individual effects. Under these circumstances, blocking any one of the three secretagogues would greatly diminish the effect of the remaining two. Not only does this latter mechanism explain the cimetidine effect, but it also may explain why atropine and vagotomy partially block the effect of histamine and gastrin on acid secretion, and also why gastrin and acetylcholine potentiate the effect of histamine.

Pharmacology of Cimetidine

To determine the pharmacokinetics of cimetidine,[4] a dozen fasted volunteers were given a 300 mg dose intravenously, intramuscularly or orally, and blood levels were measured at various times thereafter (Figure 3). Cimetidine was rapidly absorbed when given orally, and peak blood levels of 1.3 μg per ml were achieved within half an hour. Higher blood levels were, of course, obtained after parenteral administration, but by two hours the three curves were no longer appreciably different. Thus, while less drug reached the

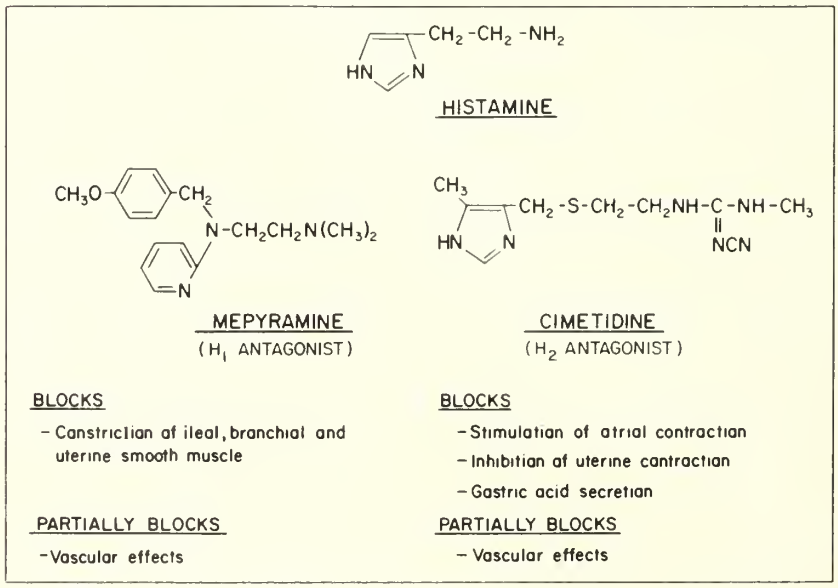

Figure 1.—Chemical structures of histamine, mepyramine (a prototype H_1-receptor antagonist) and cimetidine (an H_2-receptor antagonist). The histamine effects listed here which are blocked by H_1- and H_2-receptor antagonists have been defined largely in experiments in animals. In humans, we are still learning the effect of these drugs.

systemic circulation following oral as compared to parenteral administration, most patients had blood levels adequate to suppress acid secretion (at least 0.5 μg per ml) for four hours following all three routes of administration.

Administration of cimetidine with food delays the appearance of peak levels in blood, but total absorption is not altered and cimetidine need not therefore be administered in the fasting state.[5] There is, however, preliminary evidence that cimetidine absorption is modestly impaired by antacids.[6] Although these findings need verification, they should be considered when prescribing both cimetidine and antacids to patients with virulent peptic ulcer disease. Cimetidine-induced inhibition of acid secretion is directly related to blood levels rather than intragastric concentration, and the effects of a single 300 mg dose on gastric acid secretion are summarized in Table 1.[7]

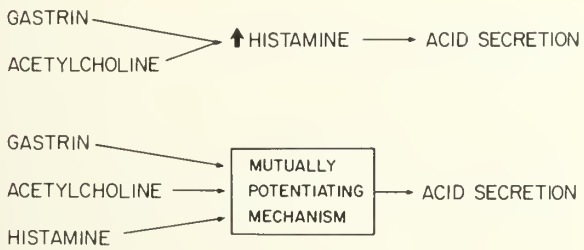

Figure 2.—Schematic representation of proposed mechanisms of gastric acid secretion and cimetidine action. In the top panel, gastrin and acetylcholine augment histamine production or release in gastric mucosa, which in turn stimulates acid secretion. Cimetidine, by blocking the effect of histamine, the final common mediator, blocks also the effect of gastrin and acetylcholine. In the bottom panel, gastrin, acetylcholine and histamine are mutual potentiators of acid secretion. Cimetidine, by blocking the effect of histamine, also substantially decreases the response to gastrin and acetylcholine.

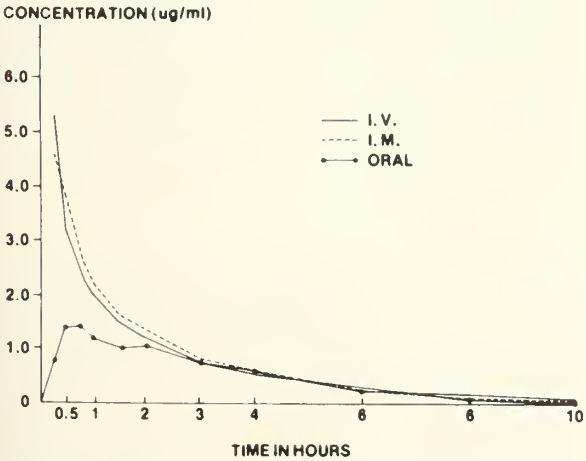

Figure 3.—Mean blood levels after administration of 300 mg of cimetidine by various routes (reprinted with permission from Walkenstein et al[4]).

TABLE 1.—*Effects of a Single Oral 300 mg Dose of Cimetidine on Gastric Acid Secretion*

- Basal secretion is suppressed by 95 percent for five hours
- Nocturnal secretion is suppressed by 80 percent for five hours
- Food-stimulated secretion is suppressed by 70 percent for three hours

TABLE 2.—*Recommended Cimetidine Dosage*

Normal adults	
	Orally: 300 mg with or before each meal and at bedtime
	Parenterally: 300 mg intravenously every six hours
Special circumstances	
	Initial dosage should be reduced by half in patients with renal failure whether or not receiving dialysis
	Patients with pronounced acid hypersecretion (for example, Zollinger-Ellison syndrome) may require larger doses or supplementation with anticholinergics, or both

Less information is available regarding the effect of cimetidine on secretion of pepsin and intrinsic factor. It appears that while cimetidine has little effect on basal secretion of either of these substances, betazole-stimulated output of both is substantially decreased.[8] The effect of long-term cimetidine administration on vitamin B_{12} absorption is unknown.

About 50 percent to 70 percent of cimetidine is excreted unchanged in the urine. Up to 30 percent of a single dose is metabolized in the liver, the primary metabolite being a sulfoxide. A greater proportion is metabolized following an oral dose than following a parenteral dose, presumably because the oral dose must pass through the liver before entering the systemic circulation. Cimetidine metabolites are also excreted in the urine, with less than 2 percent of the drug appearing in bile.

This information has been translated into the dosage recommendations shown in Table 2. For most patients, a 300 mg dose given just before or with each meal will effectively inhibit food-stimulated acid secretion and an additional bedtime dose will effectively abolish nighttime secretion. When oral administration is impossible, 300 mg given intravenously every six hours is an effective alternative.

In patients with moderate to severe renal in-

sufficiency (a serum creatinine concentration of 3 mg per dl), initial dosage should be reduced by about half. Hemodialysis is reportedly effective in removing circulating cimetidine, but the total quantity of drug removed by dialysis is small.[9] Therefore, even on the day of dialysis, cimetidine dosage should be reduced. In 30 percent to 50 percent of patients with the Zollinger-Ellison syndrome the response to the usual dose of 1.2 grams per day is not adequate and often an increase in cimetidine dosage is required. Preliminary findings also suggest that supplementation of cimetidine with an anticholinergic agent may be more effective than increasing cimetidine dosage alone in such patients.[10]

Clinical Efficacy of Cimetidine

In assessing the efficacy of cimetidine, we are fortunate in that a large number of properly conducted, prospective controlled trials have already been completed. In fact, cimetidine trials in which the results of therapy have been monitored by endoscopy have provided us with more information on the healing of peptic ulcers than had accumulated in the previous 100 years.[11] For the sake of convenience, I have grouped those disorders in which cimetidine has been used according to the scheme shown in Table 3.

TABLE 3.—*Clinical Uses of Cimetidine*

- Acid peptic disorders
  - Disorders in which cimetidine is both effective and FDA approved
    - Duodenal ulcer, acute therapy
    - Zollinger-Ellison syndrome
  - Disorders in which cimetidine is effective but not FDA approved
    - Duodenal ulcer, maintenance therapy
    - Pancreatic insufficiency (adjunct to oral enzymes)
    - Fulminant hepatic failure (prevention of gastrointestinal hemorrhage)
  - Disorders in which cimetidine is probably effective but not FDA-approved
    - Gastric ulcer, acute and maintenance therapy
    - Reflux esophagitis
    - "Stress" gastritis
    - Short-bowel syndrome (with acid hypersecretion)
- Non-acid peptic disorders in which cimetidine has been tried
  - Pruritus
    - Myeloproliferative disorders
    - Uremia
    - Cholestasis
  - Carcinoid syndrome

FDA = Food and Drug Administration

Acid Peptic Disorders for Which Cimetidine Has Been Proved Effective and Is FDA Approved

Duodenal Ulcer

Ten controlled trials have now established beyond a reasonable doubt that cimetidine accelerates the healing of duodenal ulcers when compared with placebo, and it has been approved by the United States Food and Drug Administration (FDA) for short-term use (not to exceed six weeks) in this disorder. Cimetidine is as effective as intensive antacids, but no more so.[12-17]

Zollinger-Ellison Syndrome

Although the Zollinger-Ellison syndrome is difficult to study in a controlled fashion, there is little doubt that cimetidine is effective in this disorder. It has been shown to abolish pain, diarrhea and weight loss, and to heal ulcers. Cimetidine may represent an alternative to total gastrectomy in some patients and is FDA approved for long-term use in this disorder. Cimetidine or other H_2-receptor antagonists appear equally as effective in the treatment of acid hypersecretion which may accompany mastocytosis or basophilic leukemia.[18-20]

Acid Peptic Disorders for Which Cimetidine Has Been Proved Effective but Is Not FDA Approved

Duodenal Ulcer Maintenance Treatment

Several controlled trials have shown that 400 to 800 mg of cimetidine given daily for 6 to 12 months will diminish the chance of ulcer relapse. Relapse in placebo groups was as high as 80 percent while that in the cimetidine groups averaged about 20 percent. When cimetidine was stopped, ulcers recurred as frequently as in the control group, so the natural history of the disease was only temporarily modified, not permanently altered.[16,21-25]

Pancreatic Insufficiency

Oral enzyme preparations used in pancreatic insufficiency are inactivated by gastric acid and adjunctive therapy with cimetidine appears superior to either adjunctive antacid therapy or enteric coated enzymes in improving fat absorption in adults.[26] Not only does cimetidine inhibit acid inactivation, but it greatly reduces the overall volume of gastric secretion. This minimizes dilution of the replacement enzymes and may explain cimetidine's superiority over antacids. Cimetidine

has also been shown to be similarly effective in the treatment of pancreatic insufficiency due to cystic fibrosis in children.[27]

Fulminant Hepatic Failure

In patients with fulminant hepatic failure, a trial of cimetidine did not alter survival, but it did virtually abolish major gastrointestinal hemorrhage when compared with controls. Antacids are also probably effective in this setting but were unfortunately used in an inadequate dose in this study.[28]

Acid Peptic Disorders for Which Cimetidine Possibly Is Effective but Is Not FDA Approved

Gastric Ulcer

Four controlled trials have yielded conflicting results regarding the value of cimetidine. In two instances cimetidine was as effective as intensive antacid therapy, but the value of antacids themselves in this disorder has not been established. Taken together, these studies suggest that cimetidine probably has some small advantage over placebo, but the results are clearly not so dramatic as with duodenal ulcer disease. This is not really surprising since gastric ulcer, unlike duodenal ulcer, is not usually accompanied by acid hypersecretion.[29-32]

Reflux Esophagitis

Three studies on the use of cimetidine have provided somewhat conflicting results. In two of the three, cimetidine decreased symptoms compared with placebo but failed to improve the histologic or endoscopic appearance of the esophagus. The third study showed exactly the opposite findings. Taken together, the results suggest that cimetidine, like antacids, may improve symptoms and possibly esophagitis in some patients when used in conjunction with other antireflux measures.[33-35]

Stress Gastritis

Gastrointestinal hemorrhage due to superficial gastroduodenal erosions—so-called stress gastritis—is a potential problem in all severely ill patients. In any one patient, the incidence of significant bleeding increases with the number of risk factors including respiratory failure, renal failure, hepatic failure, hypotension, peritonitis and sepsis. Prophylactic antacids have been reported to decrease the incidence of hemorrhage in patients in intensive care units. Based on these findings, as well as the results of cimetidine therapy in patients with fulminant hepatic failure, who characteristically have multiple risk factors, one might anticipate that cimetidine would also be beneficial in the prevention of stress gastritis in other patient groups. Preliminary, uncontrolled observations suggest this may be true.[36-39]

Short-Bowel Syndrome

Patients in whom resection of most of the bowel has been done may have dramatic acid hypersecretion, although it is frequently transient. This excess acid further compromises the ability of the remaining gut to absorb nutrients and may lead to fluid and electrolyte imbalance. Cimetidine has been reported to be dramatically helpful in several such cases, but experience is still too limited to make any general recommendation.[40]

Use of Cimetidine in Non-Acid Peptic Disorders

Pruritus

There is accumulating evidence that the human vasculature has both H_1 and H_2 receptors. This has provided the rationale for the use of cimetidine as well as conventional antihistamines in pruritic states believed to be related to histamine. For example, pruritus occurs in approximately half of patients with polycythemia vera and other myeloproliferative disorders and is frequently accompanied by elevated blood histamine levels. Conventional antihistamines are only partially effective in controlling symptoms, and there are now several reports of such patients with intractable pruritus who have responded to cimetidine. This has not been studied in a controlled fashion.[41,42] Cimetidine has been studied in a controlled, prospective fashion in patients with chronic idiopathic urticaria. Cimetidine, either alone or in combination with a conventional antihistamine, was no more effective than the conventional antihistamine alone.[43] Preliminary results also suggest that neither the pruritus associated with cholestasis[44] nor the pruritus associated with uremia[45] responds to cimetidine.

Carcinoid Syndrome

There is one dramatic report of a patient with metastatic gastric carcinoid and elevated urinary histamine levels who had had four flushing epi-

sodes per day for 22 years. While treatment with conventional antihistamines or cimetidine alone was only partially successful in relieving the symptoms, treatment with both together virtually abolished the flushing. This supports the presence of both H_1 and H_2 vascular receptors and suggests that certain carcinoid subgroups with hyperhistaminemia may benefit from combined H_1 and H_2 receptor blockade.[46]

Cimetidine Side Effects

Before discussing the side effects of cimetidine, a few general comments may be helpful. Before marketing of the drug in this country in 1977, approximately 3,000 patients had received cimetidine, and many of these were in controlled trials under close observation for evidence of toxicity. Since 1977 more than 2 million patients have received the drug in this country alone, and, in general, our postmarketing surveillance has been fairly keen. Despite this total of 50,000 patient-years of observation, life-threatening toxicity has not been reported and much of our information regarding side effects is at present in the form of letters. Therefore, short-term toxicity appears to be gratifyingly low. Any statement regarding long-term effects must obviously await more experience. I shall discuss cimetidine side effects by organ system.

Renal

Cimetidine produces a small decrease in creatinine clearance without any change in inulin clearance or in other renal function studies. Serum creatinine levels rise slightly with therapy, but rarely exceed the upper limit of normal and fall promptly after the drug is stopped. There is no evidence yet of serious renal toxicity.[47]

Endocrine

In animals, cimetidine has been shown to be a weak nonsteroidal antiandrogen, and prolonged administration results in shrinkage of the testes, prostate and seminal vesicles.[48,49] In men, cimetidine therapy has been shown to lower sperm count by 43 percent, decrease pituitary output of luteinizing hormone in response to luteinizing hormone releasing factor and produce gynecomastia.[50] Infertility, consequently, is a potential side effect of prolonged cimetidine therapy. Cimetidine, particularly when given parenterally, may elevate prolactin levels in both men and women and several cases of galactorrhea have been reported.[51-54] Finally, there is one reported case of primary hyperparathyroidism in which cimetidine apparently lowered circulating parathormone levels to normal,[55] and in a small group of normal volunteers there was minor deterioration in glucose tolerance curves following cimetidine administration, although none became frankly abnormal.[56]

Neurologic

More than 57 cases have been reported in which cimetidine administration appeared to produce a reversible metabolic encephalopathy varying in severity from mild restlessness and confusion to hallucinations, agitation and in some cases coma.[57-64] This encephalopathy has typically been described in older patients with serious illnesses, especially renal failure, and some observers have questioned its existence as a distinct entity. Nonetheless, there are several cases in which the temporal relationship of encephalopathy to cimetidine administration and recurrence with rechallenge strongly implicate cimetidine as the cause. One group of investigators has observed this disorder only in patients with trough blood levels (that is, blood levels drawn just before repeat administration of the drug) exceeding 1.25 μg per ml and speculate that the disorder results from cimetidine overdosage.[62] Others, however, have noted mental changes in patients with blood levels as low as 0.13 μg per ml,[63] and in normal persons ingesting large amounts of the drug, serum levels greater than 50 μg per ml have been achieved without neurological abnormalities.[64] Therefore, the metabolic encephalopathy may reflect not only high blood levels, but also abnormally high permeability of the blood-brain barrier to cimetidine. This is supported indirectly by the observation that cerebrospinal fluid levels of cimetidine in encephalopathic patients have averaged about a quarter of simultaneously drawn blood levels,[62] whereas cimetidine does not penetrate the central nervous system in animals. Regardless of cause, the encephalopathy seems to have been quickly and completely reversible following discontinuation of the drug.

Hematologic

While cimetidine has not caused fatal agranulocytosis as did metiamide, there are now about 30 cases in which it has been associated with

reversible leukopenia. These patients have generally had complex medical problems, frequently renal failure, and in many instances it has been difficult to link the leukopenia convincingly to the drug.[65] There are also isolated case reports of thrombocytopenia associated with cimetidine administration.[66]

Cardiac

Several cases of reversible bradycardia have been attributed to cimetidine.[67]

Gastrointestinal

Cimetidine administration has been associated with diarrhea (which in some instances was severe and recurred with readministration),[68] pancreatitis[69,70] and duodenal erosions (which in at least one instance appeared related to a fungal infection).[71,72] Also, while the overall incidence of abnormal liver function test results in adults taking cimetidine is no greater than in controls,[48] cimetidine administration appears to have caused a hepatitis-like reaction in at least one adult[73] and is implicated in several cases of mild, reversible cholestasis in children.[74]

Immunologic

Cimetidine has been reported to augment the blastogenic response of human lymphocytes bearing H_2 receptors to phytohemagglutinin and pokeweed mitogen[75] *in vitro,* and preliminary results suggest that cimetidine may alter delayed hypersensitivity in normal adults.[76] The earlier suggestion that cimetidine accelerated renal allograft rejection has not been borne out by more careful observation.[77]

Hypersensitivity

One case of Stevens-Johnson syndrome,[78] several cases of drug fever,[79] and one case of facial edema and laryngospasm[80] have been attributed to cimetidine.

Drug-Drug Interaction

Seventeen cases have now been reported to the FDA in which cimetidine has potentiated the hypoprothrombinemic effect of warfarin.[81]

Cost

No drug assessment can be considered complete without reference to cost, and Table 4 summarizes the cost to the patient of a six-week course of cimetidine (1.2 grams per day) and intensive antacid therapy (140 mEq of a potent antacid taken one and three hours after each meal and at bedtime). Although cimetidine is slightly more expensive, two qualifying points need to be made. First, these represent patient costs at the University of California, San Francisco, Pharmacy only. Elsewhere, the prices of both cimetidine and antacids may be considerably higher. Second, this cost applies only if the whole six week supply of medication is purchased at once. Purchased one bottle at a time, antacid therapy would cost $80 to $150 depending on the brand. Therefore, cost need not be a major factor in deciding between antacids and cimetidine. The daily cost of 1.2 grams of cimetidine given intravenously (Table 4) is obviously more than for the tablets, but not excessive when compared with other costs of hospital stays.

TABLE 4.—*Cimetidine Cost*

	Total cost for six weeks' treatment (UCSF Pharmacy)*
Cimetidine (300 mg with meals and at bedtime)	$37.00
Antacids (140 mEq one and three hours after each meal and at bedtime)	$12.90
	Total cost for one day's treatment*
Cimetidine (injectable) (300 mg every six hours)	$8.40

*These figures represent the cost to the patient of a six-week supply of cimetidine and antacids purchased at once at the University of California, San Francisco, Pharmacy. These figures may be considerably higher at private pharmacies, if cimetidine or antacids are purchased in smaller amounts, or if certain less potent antacids are selected.

Conclusions

Given all this diverse information, what kind of conclusions can be drawn regarding the place of cimetidine in our therapeutic armamentarium?

Cimetidine Versus Antacids

With respect to most disorders related to acid secretion, cimetidine should not be thought of as being more effective than antacids. Rather, it simply differs in its mechanism of action. The fundamental difference, of course, is that antacids neutralize luminal acid, whereas cimetidine prevents acid secretion. In the case of ulcer disease and gastritis, we do not know whether this is an important distinction; that is, we do not know

what damage the hydrogen ion does on its way to the lumen. Clinically, antacids and cimetidine seem to be equally effective under most circumstances.

However, there are special instances in which the distinction between the mechanism of action of cimetidine and antacids may be important. For example, reduction of the volume of gastric secretion, as well as the amount of acid, may play a role in cimetidine's beneficial effect in pancreatic insufficiency and its superiority to antacids. Also, in patients with pronounced acid hypersecretion on nasogastric suction, severe metabolic alkalosis and fluid-electrolyte imbalance frequently develop. This can be prevented by cimetidine but not antacids. Under these special circumstances, the selective advantage of cimetidine can be exploited.

Recommendations Regarding Cimetidine Usage

Cimetidine constitutes appropriate initial therapy for patients with duodenal ulcer disease, particularly patients with complications and severe and frequent pain. Cimetidine also constitutes appropriate long-term therapy for patients with pronounced acid hypersecretion due to the Zollinger-Ellison syndrome. The choice between antacids and cimetidine for ulcer patients depends on physician philosophy and patient convenience and expectation. The decision to operate on patients with Zollinger-Ellison syndrome for removal of their tumor or total gastrectomy must be made on a case-by-case basis depending on operative risk and tumor location.

I think a reasonable case can be made for cimetidine use in special circumstances such as patients with the short-bowel syndrome and notable acid hypersecretion and in patients with pancreatic insufficiency unresponsive to enzyme replacement alone or enzymes plus antacids. I think it also may constitute reasonable therapy in patients with fulminant hepatic failure and possibly also in patients with other catastrophic illnesses in which stress-induced gastrointestinal hemorrhage is likely to be a problem. However, this latter instance is exactly the situation in which toxicity, particularly encephalopathy, is most likely to occur and is hardest to recognize. Therefore, dosage should be titrated, if possible, according to the pH of the nasogastric aspirate; toxicity, particularly encephalopathy, should be watched for, and blood levels should be checked when possible.

I personally think it is premature to use cimetidine in the long-term maintenance therapy of chronic disorders such as peptic ulcer disease and reflux esophagitis, although individual cases may constitute exceptions. It also is inappropriate for patients with acute or chronic undiagnosed abdominal problems.

As continued postmarketing surveillance provides us with more information regarding short-term and long-term side effects and as we accumulate more information about cimetidine's effectiveness in acid peptic and non-acid peptic disease, these guidelines will undoubtedly change.

REFERENCES

1. Beaven MA: Histamine. N Engl J of Med 294:30-36, 320-325, 1976

2. Brimblecombe RW, Duncan WAM, Durant GJ, et al: Characterization and development of cimetidine as a histamine H_2-receptor antagonist. Gastroenterology 74:339-347, 1978

3. Gardner JD, Jackson MJ, Batzri S, et al: Potential mechanisms of interaction among secretagogues. Gastroenterology 74: 348-354, 1978

4. Walkenstein SS, Dubb JW, Randolph WC, et al: Bioavailability of cimetidine in man. Gastroenterology 74:360-365, 1978

5. Bodemar G, Norlander B, Fransson L: The absorption of cimetidine before and during maintenance treatment with cimetidine and the influence of a meal on the absorption of cimetidine—Studies in patients with peptic ulcer disease. Br J Clin Pharmacol 7:23-31, 1979

6. Bodemar G, Norlander B, Walan A: Diminished absorption of cimetidine caused by antacids (Letter). Lancet 1:444-445, 1979

7. Richardson CT: Effect of H_2-receptor antagonists on gastric acid secretion and serum gastrin concentration—A review. Gastroenterology 74:366-370, 1978

8. Binder HJ, Donaldson RM Jr: Effect of cimetidine on intrinsic factor and pepsin secretion in man. Gastroenterology 74:371-375, 1978

9. Vajiri ND, Ness RL, Barton CH: Hemodialysis clearance of cimetidine. Arch Intern Med 138:1685-1686, 1978

10. McCarthy DM, Hyman PE: Cholinergic influence on gastric acid secretion in the Zollinger-Ellison syndrome (abstract). Gastroenterology 76:1198, 1979

11. Fordtran JS: Placebos, antacids and cimetidine for duodenal ulcer. N Engl J Med 298:1081-1083, 1978

12. Gray GR, Smith IS, McKenzie I, et al: Oral cimetidine in severe duodenal ulceration—A double-blind controlled trial. Lancet 1:4-7, 1977

13. Binder HJ, Cocco A, Crossley RJ, et al: Cimetidine in the treatment of duodenal ulcer—A multicenter double-blind study. Gastroenterology 74:380-388, 1978

14. Ippoliti AF, Sturdevant RA, Isenberg RI, et al: Cimetidine versus intensive antacid therapy for duodenal ulcer—A multicenter trial. Gastroenterology 74:393-395, 1978

15. Gillies RR, Archambault A, Kinnear DG, et al: Controlled comparison of two dosage regimens of cimetidine in duodenal ulcer—A multicenter study. Gastroenterology 74:396, 1978

16. Hetzel DJ, Hansky PJ, Shearman DJ, et al: Cimetidine treatment of duodenal ulceration—Short-term clinical trial and maintenance study. Gastroenterology 74:389-392, 1978

17. Winship DH: Cimetidine in the treatment of duodenal ulcer —Review and commentary. Gastroenterology 74:402-406, 1978

18. McCarthy DM: Report on the United States experience with cimetidine in Zollinger-Ellison syndrome and other hypersecretory states. Gastroenterology 74:453-456, 1978

19. Swisher RW, Mueller JM, Halloran G: Basophilic leukemia presenting as gastroduodenal ulceration—Effect of H_2-receptor blockade. Am J Dig Dis 23:952-955, 1978

20. Feldman EJ, Isenberg JI: Effects of cimetidine on gastric acid hypersecretion, steatorrhea, and bone marrow function in a patient with systemic mastocytosis. N Engl J Med 295:1178-1179, 1976

21. Gray GR, Smith IS, McKenzie I, et al: Long-term cimetidine in the management of severe duodenal ulcer dyspepsia. Gastroenterology 74:397-401, 1978

22. Gudman-Hoyer E, Jenson KB, Krag E, et al: Prophylactic effect of cimetidine in duodenal ulcer disease. Br Med J 1:1095-1097, 1978

23. Blackwood WS, Maudgal DP, Northfield TC: Prevention by bedtime cimetidine of duodenal ulcer relapse. Lancet 1:626-627, 1978

24. Bodemar G, Walan A: Maintenance treatment of recurrent peptic ulcer by cimetidine. Lancet 1:403-407, 1978

25. Mekel RC: Long-term treatment with cimetidine. S Afr Med J 54:1089-1091, 1978

26. Regan PT, Malagelada JR, DiMagno ET, et al: Comparative effect of antacids, cimetidine and enteric coating on the therapeutic response to oral enzymes in severe pancreatic insufficiency. N Engl J Med 297:854-858, 1977

27. Cox KL, Isenberg JN, Osher AB, et al: The effect of cimetidine on maldigestion in cystic fibrosis. J Pediatr 94:488-492, 1979

28. MacDougall BR, Bailey RJ, Williams R: H_2-receptor antagonists and antacids in the prevention of acute gastrointestinal hemorrhage in fulminant hepatic failure—Two controlled trials. Lancet 1:617-619, 1977

29. Frost F, Rehbek I, Rune SJ, et al: Cimetidine in patients with gastric ulcer—A multicenter controlled trial. Br Med J 2:795-797, 1977

30. Englert E Jr, Freston JW, Graham DY, et al: Cimetidine, antacid, and hospitalization in the treatment of benign gastric ulcer—A multicenter double-blind study. Gastroenterology 74:416-425, 1978

31. Dyck WP, Belsite A, Fleshler B, et al: Cimetidine and placebo in the treatment of benign gastric ulcer—A multicenter double-blind study. Gastroenterology 74:410-415, 1978

32. Freston JW: Cimetidine in the treatment of gastric ulcer—Review and commentary. Gastroenterology 74:426-430, 1978

33. Powell-Jackson P, Barkley H, Northfield TC: Effect of cimetidine in symptomatic gastroesophageal reflux. Lancet 2:1068-1069, 1978

34. Wesdorp E, Bartelsman J, Pape K, et al: Oral cimetidine in reflux esophagitis—A double-blind controlled trial. Gastroenterology 74:821-824, 1978

35. Behar J, Brank DL, Brown FC, et al: Cimetidine in the treatment of symptomatic gastroesophageal reflux—A double-blind controlled trial. Gastroenterology 74:441-448, 1978

36. Dunn DH, Rischer RC, Silver SE, et al: The treatment of hemorrhagic gastritis with cimetidine. Surg Gynecol Obstet 147:737-739, 1978

37. Bulrick MP, Wetherille RE, Onstad GR, et al: Control of acute gastroduodenal hemorrhage with cimetidine. Surgery 84:510-518, 1978

38. MacDonald AS, Pyne DA, Freemon AN, et al: Upper gastrointestinal bleeding in the intensive care unit. Can J Surg 21:81-84, 1978

39. Martin LF, Stalock DK, Simonowitz DA, et al: Failure of cimetidine prophylaxis in the critically ill. Arch Surg 114:492-496, 1979

40. Cortot A, Fleming CR, Malagelada JR: Improved nutrient absorption in short-bowel syndrome with gastric hypersecretion. N Engl J Med 300:79-80, 1979

41. Easton P, Galbraith PR: Cimetidine treatment of pruritus in polycythemia vera (Letter). N Engl J Med 299:1134, 1978

42. Hess CE: Cimetidine for the treatment of pruritus (Letter). N Engl J Med 300:370, 1979

43. Commens CA, Greaves MW: Cimetidine in chronic idiopathic urticaria—A randomized double-blind study. Br J Dermatol 99:675-679, 1978

44. Harrison AR, Littenberg G, Goldstein L, et al: Pruritus, cimetidine and polycythemia (Letter). N Engl J Med 300:433, 1979

45. Zappacosta AR, Hauss D: Cimetidine doesn't help pruritus of uremia (Letter). N Engl J Med 300:1280, 1979

46. Roberts LJ, Marney SR, Oates JA: Blockade of the flush associated with metastatic gastric carcinoid by combined histamine H_1 and H_2 receptor antagonists—Evidence of an important role of H_2 receptors in human vasculature. N Engl J Med 300:236-238, 1979

47. Dubb JW, Stote RM, Familiar PG, et al: Effect of cimetidine on renal function in normal man. Clin Pharmacol Ther 24:76-83, 1978

48. Kruss DM, Littman A: Safety of cimetidine. Gastroenterology 74:478-483, 1978

49. Winters SJ, Banks JL, Louaux DL: Cimetidine as an antandrogen in the rat. Gastroenterology 76:504-508, 1979

50. Van Thiel DH, Gavaler JS, Smith WI Jr, et al: Hypothalamic-pituitary gonadal dysfunction in men using cimetidine. N Engl J Med 300:1012-1015, 1979

51. Carlson HE, Ippoliti AF: Cimetidine, an H_2-antihistamine, stimulates prolactin secretion in man. J Clin Endocrinol Metab 45:367-370, 1977

52. Bohnet HG, Greiwe M, Hanker JP, et al: Effects of cimetidine on prolactin, LH, and sex steroid secretion in male and female volunteers. Acta Endocrinol 88:428-434, 1978

53. Bateson MC, Browning MC, Maconnachie A: Galactorrhea with cimetidine (Letter). Lancet 2:247, 1977

54. Burland WL, Gleoclie RI, Lee RM, et al: Prolactin responses to cimetidine. Br J Clin Pharmacol 7:19-21, 1979

55. Kaufman S Milstien S: Does cimetidine inhibit parathyroid hormone secretion? (Letter). N Engl J Med 300:174, 1979

56. Jeffreys DB, Vale JA: Effect of cimetidine on glucose handling (Letter). Lancet 1:383, 1978

57. McMillan MA, Ambis D, Siegel JH: Cimetidine and mental confusion (Letter). N Engl J Med 298:284, 1978

58. Devlin JT: Coma and cimetidine therapy (Letter). J Maine Med Assoc 69:160, 1978

59. Bacrgalupo A, Van Lint MT, Marmont AM: Cimetidine-induced coma (Letter). Lancet 2:45, 1978

60. Agarwal SK: Cimetidine and visual hallucinations (Letter). JAMA 240:214, 1978

61. Wood CA, Isaacson MI, Hibbs MS: Cimetidine and mental confusion (Letter). JAMA 239:2550, 1978

62. Schentag JJ, Cerra FB, Calleri G, et al: Pharmacokinetic and clinical studies in patients with cimetidine-associated mental confusion. Lancet 1:177-181, 1979

63. Niselnicki SR, Waller JL, Finlayson DC: Physostigmine revisal of cimetidine-induced mental confusion (Letter). JAMA 241:826-827, 1979

64. Flind AC, Rowley-Jones D: Mental confusion and cimetidine (Letter). Lancet 1:379, 1979

65. Freston JW: Cimetidine and granulocytopenia. Ann Intern Med 90:264-265, 1979

66. McDaniel JL, Stern JJ: Thrombocytopenia with cimetidine therapy (Letter). N Engl J Med 300:864, 1979

67. Reding P, Devroede C, Barbier P: Bradycardia after cimetidine (Letter). Lancet 2:1227, 1977

68. Field R, Meyer GW: Diarrhea from cimetidine (Letter). N Engl J Med 299:262, 1979

69. Hadas N, Wapnick S, Grosberg SJ: Cimetidine in pancreatitis (Letter). N Engl J Med 299:487, 1978

70. Arnold F, Doyle PJ, Bell G: Acute pancreatitis in a patient treated with cimetidine (Letter). Lancet 1:382, 1978

71. Al-Nakib B: Duodenal erosions during cimetidine therapy (Letter). Lancet 1:607, 1979

72. Lombardo L, Pera A, Genovesio L, et al: Duodenal mycosis during carbenoxolone and cimetidine treatment (Letter). Lancet 1:607-608, 1979

73. Villenueve JP, Warner HA: Cimetidine hepatitis. Gastroenterology 77:143-144, 1979

74. Lilly JR, Hitch DC, Javitt NB: Cimetidine cholestatic jaundice in children. J Surg Res 24:384-387, 1978

75. Gifford RR, Hatfield SM, Schimedtke JR: Cimetidine-induced modulation of human lymphocyte blastogenesis (abstract). Proc Am Assoc Cancer Res 20:164, 1979

76. Avella J, Madsen JE, Binder HJ, et al: Effect of histamine H_2-receptor antagonists on delayed hypersensitivity (Letter). Lancet 1:624-626, 1978

77. Charpenter B, Fries D: Cimetidine and renal allograft rejection (Letter). Lancet 1:1265, 1978

78. Ahmed AH, McLarty DG, Sharma SK, et al: Stevens-Johnson syndrome during treatment with cimetidine (Letter). Lancet 2:433, 1978

79. Nisticko G, Toiroti D, deSarro A, et al: Mechanism of cimetidine-induced fever (Letter). Lancet 2:265, 1978

80. Delaunoes L: Hypersensitivity to cimetidine (Letter). N Engl J Med 300:1216, 1979

81. Silver BA, Bell WR: Cimetidine potentiation of the hypoprothrombinemic effect of warfarin (Letter). Ann Intern Med 90:348-349, 1979

Important Advances in Clinical Medicine

Epitomes of Progress — Neurosurgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in neurosurgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in neurosurgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurosurgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Microsurgical Treatment of Ischemic Cerebrovascular Disease

THE APPLICATION of microsurgical techniques to the problem of cerebral ischemia can improve collateral circulation to the brain. It is now possible to create new pathways of blood flow by surgical anastomosis of arteries that normally supply the scalp to intracranial cerebral vessels. The most common procedure produces an end-to-side anastomosis between the superficial temporal artery and a branch of the middle cerebral artery (STA-MCA). Internal diameters of the vessels involved range from 0.8 mm to 1.5 mm, necessitating the use of an operating microscope and 10-0 monofilamentous suture. More than 2,500 of these bypass operations have been done, and a recent review of published cases shows a patency rate greater than 90 percent with surgical morbidity and mortality both below 5 percent.

STA-MCA bypass is most applicable to patients with arterial obstructions or stenosis out of the reach of more classical cervical carotid artery reconstructive techniques. Indications for the operation include transient ischemic attacks (TIA) and reversible ischemic neurological deficits (RIND) occurring in patients with carotid artery occlusion, middle cerebral artery or carotid siphon stenosis or occlusion. Follow-up studies show a pronounced enlargement of the anastomosis demonstrable on cerebral angiography with the superficial temporal artery supplying blood to most of the middle cerebral artery distribution. Regional cerebral blood flow data indicate a 20 percent increase in flow to the previously ischemic region. Clinically, a significant reduction or complete cessation of TIA's occurs in patients, and in some instances there is a reversal of ischemic neurological deficits.

In the fall of 1977 an international, multicenter, randomized study was begun to compare the long-term results of such bypass operations with platelet suppression therapy. It is hoped that this study will answer questions regarding the relationship between surgically enhanced collateral cerebral flow and death due to stroke.

In the meantime, further developments in microneurovascular techniques continue to emerge. Revascularization of the vertebral-basilar system is now a reality utilizing the occipital artery as a donor and establishing an anastomosis to the posterior inferior cerebellar artery. In those instances where suitable donor arteries are lacking, autogenous vein and arterial grafts are being employed as well as an occasional synthetic tube graft. With

the magnification and improved illumination afforded by operating microscopes, middle cerebral artery embolectomy has experienced a resurgence. However, results seem to indicate that perhaps the STA-MCA bypass may be a more acceptable method of treatment in these cases.

STEVEN GIANNOTTA, MD

REFERENCES

Samson DS, Boone S: Extracranial-intracranial (EC-IC) arterial bypass: Past performance and current concepts. Neurosurgery 3:79-86, Jul-Aug 1978

Sundt TM Jr, Whisnant JP, Piepgras DG, et al: Intracranial bypass grafts for vertebral-basilar ischemia. Mayo Clin Proc 53:12-18, Jan 1978

Occult Spinal Dysraphism: Early and Accurate Diagnosis

OCCULT SPINAL DYSRAPHISM is a spectrum of congenital malformations that encompasses congenital dermal sinus, the tethered cord syndrome, lumbosacral lipoma and lipomyelomeningocele, diastematomyelia and other less frequent entities. Hallmarks of the condition are the low position of the conus medullaris below the second lumbar vertebra due to tethering by embryologically misplaced tissues and a posterior spina bifida. Traction on the tethered cord and occasionally compression by the abnormal tissue can produce one or more features of the neuromusculoskeletal syndrome or orthopedic syndrome, as termed by James and Lassman. A unilateral pes cavus, underdeveloped foot, shorter leg with muscle weakness and atrophy, insensitive skin, as well as urinary incontinence and scoliosis may be present at birth but more commonly evolve after a period of relatively normal development. A cutaneous anomaly such as hypertrichosis, hemangiomatous discoloration, a dimple or sinus or a subcutaneous lipoma may overlie the region of the spina bifida and intraspinal pathologic condition. The general consensus is that occult spinal dysraphism is progressive once it becomes symptomatic, but stabilizes or improves following operative relief of traction and compression and that early treatment is desirable in many cases.

The diagnosis of this condition is often missed by Pantopaque myelography which usually requires a general anesthetic for children younger than seven years. However, metrizamide myelography combined with spinal computed tomography enables the diagnosis to be made easier, earlier and more accurately. Metrizamide is a water-soluble agent with a low incidence of side effects and is completely absorbed from the dural sac; and the entire procedure is carried out under local anesthetic and sedation in all age groups. The level of the conus medullaris, the thickness of the filum terminale, the direction of caudal nerve roots as well as abnormal bands and adhesions or intraspinal filling defects are clearly displayed. Computed tomography of the metrizamide-filled dural sac details the relationships of the intraspinal structures and can identify abnormal tissues such as lipoma or cartilage on the basis of density measurements. The combined procedures yield far more information than either one done individually. Consequently, studies can be done in mildly symptomatic or even asymptomatic children with every expectation of arriving at a reliable diagnosis and treatment can be rendered before irreversible deficits develop.

BARRY N. FRENCH, MD, FRCS(C)

REFERENCES

James CCM, Lassman LP: Spinal Dysraphism: Spina Bifida Occulta. London, Butterworth and Company Publishers Limited, 1972

Harwood-Nash DCF, Fitz CR, Resjo IM, et al: Congenital spinal and cord lesions in children and computed tomographic metrizamide myelography. Neuroradiology 16:69-70, 1978

Postconcussion Syndrome

CEREBRAL CONCUSSION is a retrospective diagnosis that relates to a *transient* loss of neurologic function from which there is rapid and complete recovery without neurologic residua. It is frequently associated with a period of amnesia which relates to events immediately preceding and following the concussive event; the length of these periods of *retrograde* and *anterograde* amnesia may provide an index of the extent of the concussion. The diagnosis is established on the basis of the clinical history (transient loss of neurologic function which may or may not include unconsciousness) and absence of pathologic, chemical or radiographic findings that will either establish or invalidate the diagnosis. The presence of a concussion in itself is not a necessary harbinger of a more serious consequence in a patient's subsequent clinical course. The diagnosis of concussion simply represents clinical documentation that the extent of cerebral trauma was sufficient to transiently interrupt or disturb cerebral function.

A small but significant percentage of patients who experience a cerebral concussion as defined above will subsequently complain of recurrent headaches, dizziness, vertigo, anxiety and generalized fatigue. These symptoms, or any combination of them, have been termed the postconcussion syndrome. The process may prove to be

self-limited but is frequently refractory to any specific modality of therapy. Recent evidence indicates that a significant percentage of these patients manifest a premorbid personality disorder that appears to lend itself to the development of an apparent psychoneurotic disability. A careful determination, where possible, of premorbid personality characteristics will undoubtedly prove to be of great help in determining this possibility. Should such evidence be available, then psychiatric counseling may be helpful in some cases.

Finally, however, one must recognize the possibility for disruption of the integrity of the semicircular canals, due to a small bony fracture, resulting in a constellation of symptoms described above for the postconcussion syndrome. This may happen in the face of relatively minor trauma but must be considered a possibility when this posttraumatic symptomatology is noted. Consequently, when confronted with the clinical symptomatology of the postconcussion syndrome, one must look not only for the potential for underlying psychoneurotic disturbance but also for a disturbance in the vestibular mechanism. Such endeavors should include a thorough and detailed otologic evaluation to include electronystagmography as well as tomograms of the semicircular canals. In a small percentage of patients with the postconcussion syndrome one may therefore find an underlying anatomico-pathologic cause which may lend itself to corrective otologic surgical intervention.

MARTIN H. WEISS, MD

REFERENCE

Lidvall HF, Linderoth B, Norlin B, et al: Causes of the postconcussional syndrome. Acta Neurol Scand [Suppl] 56:3-144, 1974

Head and Neck Injury in Football

OF THE NUMEROUS sports-related injuries, head and neck injuries occurring on the football field present special problems in medicine that have to be solved in a short time by the physician in attendance. Can a player with concussion or with paresthesias and weakness in an upper extremity be allowed to reenter the game and, if so, when?

Illustrative of a common condition requiring careful judgment is what may be called a mild concussion. A football player who is shaken up may display short-term confusion, inability to remember plays, visual blurring, tinnitus, dizziness, unsteadiness, or loss of desire to return to the game. If any of these symptoms is present the player should be kept out for approximately a quarter of the game. A returning player should be observed carefully by the trainers. Some players say that they have a "normal headache" much of the time during play, but a complaint of new or unusual headache should be enough to keep any player out for the remainder of the game. In this regard, it is important that the team physician not make it generally known to players his own criteria for removal of a player.

Head injury of greater magnitude requires that a player be kept out for the remainder of the game. Included in this category would be unconsciousness even of brief duration or continuing amnesia manifested by repetitive questioning with respect to time and place. The anatomical substrates for these fairly common events are brain stem injury and anterior temporal lobe contusion respectively.

Cerebral contusion (bruising) with the possible sequelae of acute subdural or intracerebral hemorrhage should be regarded as a possibility with more prolonged unconsciousness, persistent confusion or restlessness, motor, sensory or visual paralysis, or in the event of a seizure. Players in this category should go to the hospital, and the emergency room physician should be called and informed of the medical observations. Since more severely injured players may have combined head and neck injuries, this possibility must be kept in mind during transport.

Serious neck injuries require immediate careful transportation to the hospital and may require ventilatory assistance. Any player with weakness or paresthesias in any two or all four limbs, even if the symptoms are transient should be sent to the hospital for further examination.

The nerve pinch syndrome consisting of shooting paresthesias with or without transient weakness in *one* arm occurs occasionally in many players. If these symptoms disappear in one or two minutes, the player may reenter the game, but if the same symptoms recur, the player should not play again until his condition has been evaluated by a neurosurgeon. These "stingers" or "zingers" are usually the result of contusion to the upper trunk of the brachial plexus. Occasionally they signify a cervical nerve root injury at the intervertebral foramen from a herniated cervical disc, brief subluxation, or a fracture.

Statistical studies of football injuries are less than satisfactory. However, the general belief is that because of improved headgear, there are now

fewer severe head injuries. Unfortunately, there has been a gradual return to the use of the head as a weapon, which may result in an increase in severe neck injuries with paralysis, particularly in defensive backs. Coaches should abide by the rules and teach the avoidance of "stick blocking" and "spearing." All players should be encouraged to develop maximally strong neck musculature.

JAMES B. GOLDEN, MD

REFERENCES

Schneider RC: Head and Neck Injuries in Football Mechanisms—Treatment and Prevention. Batlimore, The Williams and Wilkins Company, 1973

Robertson WC Jr, Eichman PL, Clancy WG: Upper trunk brachial plexopathy in football players. JAMA 241:1480-1482, Apr 6, 1979

Torg JS, Truex R Jr, Quedenfeld TC, et al: The National Football Head and Neck Injury Registry—Report and conclusions 1978. JAMA 241:1477-1479, Apr 6, 1979

Hemifacial Spasm or Facial Tic

HEMIFACIAL SPASM, or facial tic, is not a common disorder. However, it can be devastating to a patient's life-style and until recently has been resistant to most forms of therapy. The unilateral facial twitching is obvious to any observer, although a medical history will almost invariably show that the painless abnormal movements began in the facial muscles around the eye, spread to involve perioral muscles and sometimes platysma, and never involve shoulder or arm musculature.

The causal theories presented for this entity have been numerous and include vague congenital or acquired organic brain lesions, tumors and psychological afflictions. In the absence of a tumor, a rare cause of this problem, treatment—whether medical, psychological or surgical—has been unrewarding.

Recently, the etiologic concept of compression of the facial nerve by branches of normal but tortuous cerebellar arteries has achieved considerable attention. The microscopic surgical manipulation of these vessels alone, without manipulation or damage to the facial nerve itself, has been effective in stopping the facial spasm in an overwhelming majority of patients. Although long-term follow-up has yet to occur, this operative decompression of the facial nerve appears to offer a solution to a difficult and disabling problem.

RANDALL W. SMITH, MD
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REFERENCES

Gardner WJ, Sava GA: Hemifacial spasm: Irreversible pathophysiologic state. J Neurosurg 19:240-247, Mar 1962

Jannetta PJ, Abbasy M, Maroon JC, et al: Etiology and definitive microsurgical treatment of hemifacial spasm. J Neurosurg 47:321-328, Sep 1977

Trigeminal Neuralgia

TRIGEMINAL NEURALGIA (tic douloureux) is characterized by devastating piercing pain in the face, in the distribution of one or more of the major divisions of the trigeminal nerve. Both pharmacological and surgical treatments have been unsatisfactory in the past because of a significant failure rate and toxicity with the use of drugs, and because of a significant failure rate and undesirable loss of normal sensation with surgical therapy.

Recently, Jannetta proposed that trigeminal neuralgia results from cross-compression of the trigeminal sensory nerve root, near its entry into the pons, by adjacent arterial loops usually of the superior cerebellar artery. Microsurgical separation of the offending artery from the trigeminal nerve root and insertion of a cushion, such as a small muscle fragment, between the artery and nerve has led to a very high cure rate in trigeminal neuralgia. The surgical complication rate is low and, because the nerve root is not cut, normal sensory function is preserved. This surgical procedure now provides a very high success rate, low rate of complications and a way to preserve normal sensory function. Jannetta has also suggested that cross-compression of the appropriate nerve root by adjacent arterial loops may be the cause of other forms of cranial nerve dysfunction such as glossopharyngeal neuralgia, hemifacial spasm and Meniere disease.

RONALD F. YOUNG, MD

REFERENCES

Jannetta PJ: Microsurgical approach to the trigeminal nerve for tic Douloureux. Prog Neurol Surg 7:180-200, 1976

Young RF: Trigeminal and glossopharyngeal neuralgia. *In* Conn HF, Conn RB (Eds): Current Therapy. Philadelphia, WB Saunders, 1975, pp 712-715

Craniosynostosis and Craniofacial Reconstruction

IN THE 1960's Tessier and Guiot initiated collaboration between plastic surgery and neurosurgery by utilizing a combined extracranial-intracranial approach in the treatment of orbital hypertelorism. This collaboration has continued to expand its frontiers to other varieties of craniofacial anomalies, craniosynostosis and some tumors involving the base of the skull.

In children with coronal craniosynostosis, it is no longer the goal of surgical therapy merely to open the closed cranial suture line by craniectomy. Recognition that the skull base is also involved has prompted more definitive surgical approaches that include frontal bone advancement and orbital

osteotomy. Subsequently mid-face advancement may be required in patients with the Crouzon syndrome and in some patients with the Apert syndrome.

Premature closure of the sagittal suture, which is rarely associated with orbital and facial deformities, has been satisfactorily treated for many years with strip craniectomy. A new method for treating this abnormality has been described by Jane and offers immediate correction of the deformity by reducing the anteroposterior diameter and increasing the transverse diameter.

In North America there are several craniofacial centers where the craniofacial team consists of a plastic surgeon, a neurosurgeon, a pediatrician, an ophthalmologist, an orthodontist, and other specialists who continue to refine and improve the treatment for severe craniofacial anomalies. Cosmetic results have been particularly rewarding in patients who have orbital hypertelorism and the less complicated craniofacial clefts.

JUSTIN W. RENAUDIN, MD

REFERENCES

Mohr G, Hoffman HJ, Munro IR, et al: Surgical management of unilateral and bilateral coronal craniosynostosis: 21 years of experience. Neurosurgery 2:83-92, Mar-Apr 1978

Jane JA, Edgerton MT, Futrell JW, et al: Immediate correction of saggital synostosis. J Neurosurg 49:705-710, Nov 1978

Munro IR: Orbito-cranio-facial surgery: The team approach. Plast Reconstr Surg 55:170-176, Feb 1975

Neurosurgical Aspects of Congenital Lumbar Spondylolisthesis

In a typical patient suffering with backaches from congenital lumbar spondylolisthesis, no neurological deficits are found on clinical examination. However, in a few patients neurological signs are present due to disc changes occurring most often at the level above the site of the spondylolisthesis. Lumbar spondylolisthesis is most frequent at the lumbosacral level and, in these patients, disc protrusions occur most often at the next higher level, L4-5, rather than at the site of the spondylolisthesis. These patients show more significant neurological changes than the average L4-5 disc protrusion patient. Extensor weakness of the foot of some degree will occur in 70 percent of the patients (40 percent having a complete foot drop and 30 percent a partial foot drop).

The explanation for the high incidence of foot extensor weakness is due possibly to three factors: (1) The fifth lumbar nerve root sometimes becomes entrapped due to entanglement in fibrous tissue along the side of the vertebra. A ligamentous band runs from the undersurface of the transverse process to the site of the vertebral body and, with the forward slippage and downward descent of the 5th lumbar vertebra, the ligament comes down on the L-5 root and may entrap it against the sacrum. (2) The forward slippage and degenerative disc changes can cause the intervertebral disc to bulge out around the periphery of the vertebral body, just like squashed putty, burying the nerve root in this bulging mass after it has emerged from the foramen. (3) A third method of producing nerve root pressure occurs when the vertebral body glides forward and downward along the inclined plane of the superior surface of the vertebral body below. With this movement, the pedicles descend on the nerve root and cause kinking as it emerges through the foramen.

In patients with spondylolisthesis and neurological deficits myelographic examination is required and will usually show complete myelographic blocks or significant nerve root deformities. Orthopedic surgeons favor spinal fusion when nonsurgical methods are not successful. Surgical therapy is most commonly used in teenagers and young adults, and rarely in the older patients. The combination of spondylolisthesis and disc protrusions, however, involves an older patient population, which usually responds successfully to simple disc excision without concomitant fusion.

The occurrence of disc protrusion in a series of patients with spondylolisthesis has been reported as 12 per 100 cases of spondylolisthesis, 2 having disc problems at the spondylolisthesis site and 10 at other intervertebral level.

LYMAN MAASS, MD

REFERENCES

Symposium on spondylolisthesis. Clin Orthop 117:1-176, 1976

Macnab I: Management of spondylolisthesis, *In* Krayenbuhl H, Maspes PE, Sweet WH (Eds): Progress in Neurological Surgery—Vol 4. Basel, Karger, 1971, pp 246-276

Acoustic Tumors

In the past two decades tremendous advances have made it possible for all physicians to recognize acoustic (schwannomas) tumors of the cerebellopontine angle without the symptoms and findings provided in classic models of this disorder.

Physicians should not wait for any or all of the symptoms of headache, nausea, vomiting or staggering gait and such findings as papilledema, facial numbness, facial palsy or ataxia to appear before being alerted to the possibility of this usually be-

nign and curable intracranial tumor. When these findings or symptoms are present the tumor has usually reached massive proportions and cannot be removed without considerable risk. This is probably related to the very slow or stuttering nature of the growth process which permits the adjacent central nervous system structures to adapt or mold without alteration in function to the slow distortion caused by the tumor.

Therefore studies should be carried out in all patients who complain of unilateral hearing loss. While highly sophisticated neurootologic test facilities are not universally available, the always accessible telephone is a superb simple screening test for detection of sensory neural hearing disorders. Frequently an early clue is provided by the simple comparison of speech perception between the right and left ear.

Telephones provide simultaneous bone and air conduction as well as an index of speech perception. Disorders of speech perception are prominent indicators of sensory-neural hearing loss or conduction impairment in the 8th nerve, the most common early finding in acoustic tumors.

Contemporary microneurosurgical techniques now make possible total tumor removal with preservation of the 7th nerve in many cases and, in an ever-increasing number of cases, preservation of the cochlear division with useful hearing.

THEODORE KURZE, MD

REFERENCES

DiTullio MV Jr, Malkasian D, Rand RW: A critical comparison of neurosurgical and otolaryngological approaches to acoustic neuromas. J Neurosurg 48:1-12, Jan 1978

Kurze T: Surgical Removal of Acoustic Neuroma, audiotape. New York City, AVENS (Audiovisual Education in Neurosurgery), 1974

Galactorrhea, Amenorrhea: An Algorithm

AN INCREASING NUMBER of patients with the syndrome complex of amenorrhea/galactorrhea are presenting to clinicians for further investigation. The development of a reliable immunoassay to assess the serum level of prolactin has enabled a greater understanding of the physiologic basis underlying this disorder in many patients. Once the diagnosis of hyperprolactinemia has been established one must pursue the potential underlying causes for this hormonal aberration. A detailed history will identify use of any of a number of pharmacological agents that may be responsible for this syndrome.

The most common cause of hyperprolactinemia relates to the use of oral contraceptives. If a patient has recently stopped using oral contraceptives or if galactorrhea develops during oral contraceptive use, withdrawal of the medication will generally result in resolution of the hyperprolactinemia within a period of two to three months. One must also consider a number of other pharmacological agents, including tranquilizers of the phenothiazine group and antidepressants. In general, discontinuation of these agents will result in resolution of the hyperprolactinemia.

If the hyperprolactinemia should persist or appears unrelated to any pharmacological agents, then one must consider a primary pituitary disorder as the underlying source. Prolactin levels in excess of 100 ng per ml are highly suggestive of a primary pituitary tumor as the underlying cause. The best subsequent test to evaluate the potential presence of a pituitary tumor is multidirectional or hypocycloidal polytomography, which will allow clear delineation of any deformation of the sella turcica. This study enables specific evaluation of distortion of the sella turcica by small intrasellar lesions. Upward projection of an intrasellar or suprasellar lesion (or both) is best evaluated by computerized tomographic scanning utilizing multiple overlapping cuts of the sella turcica and suprasellar cistern. Fractional pneumoencephalography or metrizamide cisternography may be desirable in equivocal cases. Clinical evidence for suprasellar extension may also be found by an in-depth evaluation of the visual axis using tangent screen visual field examination along with visual evoked response evaluation.

If these studies fail to show evidence of an intrasellar or suprasellar lesion, then administration of bromergocryptine will result frequently in resolution of the hyperprolactinemia and galactorrhea, with restitution of normal menses and fertility. This agent is not curative but is highly effective in suppressing the aberrant hormonal function.

If, on the other hand, evidence is obtained indicating the presence of a pituitary tumor, then transsphenoidal resection of the pituitary tumor has proved, within the past ten years, to be the most effective way to deal with this problem. This technique provides a mechanism for removal of the hyperfunctioning tumor under microscopic dissection while preserving normal adenohypophyseal and neurohypophyseal function.

Depending upon the underlying pathophysiologic process, excellent methods are available to

resolve the infertility associated with hyperprolactinemia. The ease of establishing the diagnosis by the readily available immunoassay of serum prolactin clearly opens a new and satisfying vista for the treatment of the amenorrhea/galactorrhea syndrome.

MARTIN H. WEISS, MD

REFERENCES

Antunes JL, Housepian EM, Frantz AG, et al: Prolactin-secreting pituitary tumors. Ann Neurol 2:148-153, Aug 1977

Kleinberg DL, Noel GL, Frantz AG: Galactorrhea: A study of 235 cases including 48 with pituitary tumors. N Engl J Med 296: 589-600, Mar 17, 1977

Deep Brain Electrical Stimulation to Control Intractable Pain

INTRACTABLE PAIN presents as a clinical problem across the spectrum of clinical medical disciplines. Chronic pain of both malignant and nonmalignant causes results in disability, suffering and hardship for thousands of people every year. Recent developments have indicated that chronic pain might be controlled by electrical stimulation of an antinociceptive system which is located, in part, at the paramidline structures in close relation to the back of the 3rd ventricle and the aqueduct of Sylvius.

Investigators have produced profound analgesia in laboratory animals by electrical stimulation at the above deep brain locations. Moreover, investigators have shown that the same locations have stereospecific morphine receptor sites which are productive of analgesia with microinjections of opiates. An important link in this system was the discovery of encephalins, opiate-like polypeptides which are produced endogenously. Possibly, it is speculated, electrical stimulation of deep brain structures releases encephalins, thereby producing analgesia.

The first reports of deep electrode implantation in groups of patients with intractable pain have been favorable (75 percent to 80 percent of the patients have complete or satisfactory relief of pain) for the follow-up period (up to three years). It is now thought that electrical stimulation of the paramidline structures activates a serotoninergic descending dorsal lateral spinal pathway to inhibit spinal nociceptive neurons either directly or by the release of encephalins. The addition of L-tryptophan, a serotonin precursor, in high doses to patients' diet may improve the efficacy of deep brain stimulation for the treatment of chronic pain.

Deep electrode stimulation for the treatment of chronic pain is a promising new therapeutic technique for an old and frustrating problem. It is the clinical application of a technique founded on the basis of a large body of preliminary investigative development.

ROBERT A. FELDMAN, MD

REFERENCES

Basbaum AI, Fields HL: Endogenous pain control mechanisms: Review and hypothesis. Ann Neurol 4:451-462, Nov 1978

Richardson DE, Akil H: Pain reduction by electrical brain stimulation in man—Part 2: Chronic self-administration in the periventricular gray matter. J Neurosurg 47:184-194, Aug 1977

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EDITORIALS

PSRO, Politics and Quality Assurance

IN THIS ISSUE of the journal, Alan R. Nelson offers both his impression of the Professional Standards Review Organization (PSRO) program's present illness and his guarded prognosis. As the founder of a prototype PSRO and charter member of the National PSR Council, Dr. Nelson has been a staunch advocate of PSRO as it was originally proposed by Senator Wallace Bennett. His informed commentary carries a clear message: PSRO has been progressively politicized around the issues of cost containment and public disclosure of PSRO data. This, together with numerous changes in the program's administration, has seriously jeopardized its future as a physicians' program of professional self-regulation in quality assurance.

Cost control generally is a paramount issue in the Congress and the executive branch of government, and this concern is focused particularly on the highly visible, widely publicized multibillion dollar expenditures under Medicare and Medicaid. This means that PSRO will continue to be viewed by Congress and the Department of Health, Education, and Welfare (DHEW) as an instrument for controlling those expenditures. Confrontations between the private sector of medicine and the government on this issue can at best only result in a standoff. The reason is that even when PSRO's do what they are expected to do—eliminate unnecessary hospital admissions and days of stay—there is no assurance that actual dollars will be saved.

The recent evaluation of PSRO performance by DHEW claimed that PSRO's were beginning to pay for themselves through savings of paper dollars, those assumed to have been saved as a result of reducing hospital use by Medicare and Medicaid patients.[1] However, a study of the Colorado PSRO by Private Initiative in PSRO* found no relationship between hospital utilization and hospital reimbursements by Medicare or Medicaid.[2] Specifically, in the Medicaid program, hospital use was *reduced* almost 12 percent in three years but hospital reimbursements *increased* 37 percent for the same period. Under Medicare, PSRO reviews kept the increase in hospital use to 12 percent in three years but actual reimbursements to those same hospitals for the same period went up 58 percent. The reason for the dissociation between utilization and expenditures is that the reimbursement of hospitals is negotiated by the fiscal intermediaries and the hospitals. PSRO's have no direct effect on the results of these negotiations, regardless of their effectiveness in controlling unnecessary hospital use. Consequently, attempts to prove that PSRO's are or are not "cost effective" come under the heading of political jousting, and it is not to be expected that the issue will be resolved rationally by objective and valid study.

The "assaults coming from the left," as Dr. Nelson puts it, pressing for publication of confidential physician data, will also predictably continue as a major symptom of another national issue surrounding PSRO's: explicit public accountability. There being no public representation on the National PSR Council that sets policy and reviews performance of PSRO's, public-interest groups are demanding access to profile data on physicians and hospitals. Whether such data can or cannot be released is under judicial review. If they were to be released, accurate interpretation would be difficult. The reliability and comparability of profile data have not been ascertained. Further, the data are greatly simplified and require additional clinical details for proper analysis.

Even if valid data on quality were available, impartial observers of PSRO would be hard put to attribute responsibility for the quality of hospital care to PSRO's. Dr. Nelson has posed the issue as "the delegated hospital emerging as the basic functional unit in most PSRO's" and the PSRO's "often being in an adversary position with the hospitals themselves." This situation is simply an inescapable fact of life, given the many court rulings that hospitals have a separate corporate responsibility for the quality of care. It seems

*A project sponsored by The American Association of Foundations for Medical Care, the American College of Physicians, the American Hospital Association, the American Society of Internal Medicine and, initially, the American Medical Association.

unrealistic to expect PSRO's to preempt this responsibility, and the amount of physician support of PSRO's is clearly insufficient to enable PSRO's to supplant the medical staff as the body that implements programs of quality assessment and assurance on behalf of hospital boards.

What can be concluded from this array of issues? For certain, the future of PSRO will be decided politically, not rationally. Physicians should continue to support PSRO because it is far from certain in today's political climate that the medical profession would be given another comparable opportunity in self-regulation. Given the continuing pressures to restrain hospital use, Private Initiative in PSRO concluded that "PSRO's are necessary, legally institutionalized mechanisms for protecting Medicare and Medicaid patients from inappropriate and unwarranted restrictions on needed services. . . . Such an organization, composed of physicians capable of setting reasonable standards of care and promoting their attainment, is an essential concomitant of any program, public or private, directed to containing costs."[2]

It also is evident that the federal and state governments are now in permanent partnership with physicians and hospitals in "quality assessment and quality assurance." In recognition of this fact, Private Initiative in PSRO advocated a set of principles that defined the respective responsibilities of government and the private sector in shaping the future of quality assurance. These principles state that although DHEW is legally authorized to require an accounting of the necessity and quality of services paid for by the government, it is the primary responsibility of physicians and hospitals to devise and carry out programs with the intent of improving patient care and generating objective data by which to document the assurance of quality. These data should then be transmitted to DHEW and any other public, private or third-party purchaser of care, in fulfillment of their requirements that any service paid for by them must conform to the practicable standards of the providers. By this means, quality assurance mechanisms would become publicly accountable.

The function of PSRO in quality assurance is clearly limited to assuring a basic standard of care. Most PSRO's are not now capable of assessing hospital care at this minimal level and it is doubtful that many will acquire this capability in the near future. It is manifestly unrealistic to expect PSRO to become the principal vehicle for raising hospital care to the highest practicable standards. In keeping with the requirements of the Joint Commission on Accreditation of Hospitals, it remains the responsibility of medical staffs of hospitals to assure that all patients receive the technical quality of care made possible by the steadily increasing capabilities of medical science.

These observations in no way detract from the importance of the PSRO program as the means of satisfying legitimate demands for greater accountability in the face of continuously escalating expenditures of public funds for medical care. Given necessary financial support and professional direction, PSRO may still fulfill its intended societal function of assuring that all Medicare and Medicaid patients receive an acceptable quality of care provided in the most efficient manner permitted by local circumstances.

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REFERENCES

1. Benefit-cost analysis of concurrent review, section 4, *In* Professional Standards Review Organization 1978 Program Evaluation, DHEW Pub No HCFA-03000. US Dept cf Health, Education, and Welfare, Health Care Financing Administration, Jan 1979, pp 160-173

2. Prince TR: Effect of PSRO on hospital utilization and costs, *In* Sanazaro PJ (Ed): Private Initiative in Professional Standards Review Organizations (PSRO). Ann Arbor, MI, Health Administration Press, 1978, pp 132-234

Noninvasive Evaluation of Cerebrovascular Disease

ELSEWHERE in this issue, Carson and Blaisdell present an excellent, detailed and objective analysis of the current status of various noninvasive techniques available for evaluation of extracranial cerebrovascular disease. The technology of instrumentation is advancing at a tremendous pace, and it behooves one to consider carefully the role of noninvasive testing before embarking upon a very expensive program that uses instruments which may be outmoded before adequate clinical assessment of their performance can be made.

At present, patients with *symptoms* of cerebral ischemic episodes require contrast arteriography for proper planning of therapy, especially carotid endarterectomy. Noninvasive examinations, although interesting, are not essential. Arteriography is still the definitive diagnostic procedure, and will

remain so until technological advances produce noninvasive arteriograms of equal quality. Although infrequent, complications of invasive arteriography do occur; hence, concerted efforts have quite properly been applied to the development of satisfactory noninvasive diagnostic methods in attempts to avoid unnecessary arteriograms.

Noninvasive studies are most useful for evaluating asymptomatic carotid bruits; for evaluation in patients with puzzling diagnostic problems such as dizziness, whose symptoms may or may not be due to cerebrovascular causes; as screening tests to identify stroke-prone patients; and as a simple way to follow up patients after carotid endarterectomy for any progression of disease in the unoperated or operated artery. Therefore, they aid in making more precise indications for arteriography.

Present-day noninvasive techniques fall into two basic groups: those that evaluate the functional hemodynamic significance of carotid lesions and those that outline the anatomic configurations of such plaques. Both areas of investigation suffer from the difficulty that pathologic presentations are protean, and small nonstenotic carotid lesions which may eventually ulcerate and shed the emboli responsible for cerebral ischemia do not cause any reduction in blood flow nor can they be visualized. Nevertheless, progress has been made in spite of these limitations, and directions for further advances in instrumentation are becoming apparent.

The Doppler examination is the simplest and cheapest method of evaluating the functional component of a carotid lesion. As Carson and Blaisdell point out, however, multiple sequential compression is required to improve accuracy, which complicates the test considerably and makes it highly technician dependent. Personally, I find that its usefulness is limited.

Oculoplethysmographic (OPG) techniques are widely used and probably are the most helpful examinations available at present. They all suffer from the same basic problems; namely, false negative results from bilateral lesions, and the difficulty in distinguishing severe stenoses from total occlusions. It should also be noted that the test assesses flow impediment from lesions at the origins of the great vessels off the arch to the globe of the eye; therefore, theoretically it cannot be 100 percent accurate in evaluating lesions at the carotid bifurcation. In our experience the carotid phonoangiography (CPA) component of the examination is complementary, but when used alone is unreliable because of technical factors. Overall, the OPG-CPA technique has enjoyed about 85 percent accuracy when compared with arteriograms.

Imaging techniques to display the anatomy of carotid bifurcation disease are still in the developmental stage and instrumentation is very expensive. Resolution is inadequate to define small ulcerated lesions, and calcium in the arterial wall gives false positive results. In no other area, however, is the technology advancing so rapidly. I have no doubt that eventually our current problems will be solved and that satisfactory non-invasive imaging techniques will be available. One could speculate even now, however, that computer-enhanced, intravenous contrast arteriography might suddenly render all present-day imaging techniques obsolete and unnecessary. Likewise, the functional hemodynamic component of carotid lesions may well be evaluated more accurately by analysis of Doppler wave forms and harmonics than by the OPG techniques, or for that matter by completely new methods not envisaged at present.

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Planning for Health Manpower

PLANNING FOR HEALTH MANPOWER is a complex subject which is not yet well understood. It may actually prove to have been a pioneering effort at planning of this sort within a free and independent society—a society with a new kind of interdependence because of the social and economic ramifications of expanding technology. The health care enterprise certainly has social and economic ramifications as a result of its scientific and technologic progress and it certainly has internal and external interdependencies of growing complexity. Planning within these interdependencies has proved to be neither simple nor easy. For example, a few years ago we were told that there were not going to be enough doctors and this was identified as a national crisis. Now we are being told that there are going to be too many physicians, who will not be in the right specialties or in the right places. One senses that the planning methods have been less than ade-

quate and have lacked a needed sensitivity and flexibility.

In planning for health manpower it would seem that a number of ingredients should be assessed. Among these are the geography, population and economy of the areas under consideration (whether local, regional, state or national); the services needed or perceived as needed; the numbers and types of health professionals required to render these services (and their support both professionally and financially), and the education and continuing education of the kinds and numbers of health manpower which it is anticipated will be needed and can be supported in whatever area or population that is under consideration. A major difficulty, however, is that none of these ingredients (except possibly geography) is static; rather, each is changing all the time. People move, the economy improves or worsens, the numbers and kinds of services needed change with changing life-styles and with scientific progress, and so do the roles of health professionals and the requirements and content of their education and their continuing education. In short, health manpower plans are usually out of date by the time they are completed, and the more precise and accurate the plan, the more likely this is to be so. Too, the situation addressed by the plan is almost certain to be quite different by the time any health manpower plan can be carried out, which means that the plan must almost surely be less than a complete sucess, particularly if the situation for which the plan was made no longer exists.

It would seem that more sensitivity and responsiveness is needed in planning for health manpower if it is ever to be really successful. There should be a continuing responsiveness to changes in medical science and technology, and to changes in the needs, attitudes and resources of the populations to be served and of the professionals who are to serve them—recognizing the personal and institutional independence and autonomy of all concerned. Something more akin to a treatment plan for a difficult case in medical practice appears to be what is needed. Here, decisions often have to be made on inadequate data within a framework of quickly passing time and changing events. A treatment plan is instituted promptly, the events are closely monitored and additional data are continuously collected. The treatment plan is sensitive to these new data and responds by change, modification or whatever fine tuning may be indicated.

In planning for health manpower it may also be necessary, and even prudent, to sacrifice a desirably accurate data base and a conceptually perfect and idealized plan for an approach which is more flexible, more sensitive to change in any and all of its essential ingredients, and more quickly responsive to them. Time and change wait for no man, not even for health manpower planning.

—MSMW

Water Homeostasis—Facts and Uncertainties

HOMER SMITH[1] stressed the fact that the transition from aquatic to terrestrial life was predicated on the ability of the kidneys to maintain a constant volume and composition of extracellular fluid, the so-called internal environment. Because virtually all cells of mammalian organisms are freely permeable to water, Smith's postulate requires explicitly that the kidneys—as final effectors of a complex regulatory mechanism involving, among other factors, the vascular bed and the central nervous system—maintain a constant osmolality of total body water, including both the extracellular and cellular fluid compartments.

Under normal circumstances, the osmoregulatory mechanism is very precise. In the absence of circulatory derangements, a normal neurorenal axis can maintain a virtually constant body fluid osmolality in the face of remarkably wide ranges of solute and water intake. As Verney[2] stressed, osmotic homeostasis is achieved comfortably. The osmotic threshold for release of antidiuretic hormone (ADH) from the posterior pituitary is set approximately 10 mOsm per kg of water below the normal serum osmolality;[3] in other words, tonic secretion of ADH permits us to maintain osmotic homeostasis without the need for ingesting large volumes of water.

The physiology of water metabolism, as reviewed in this issue by Weitzman and Kleeman, is a good example of a homeostatic circuit that includes afferent and efferent limbs modulated by feedback controls. Impulses from many sensory inputs, including osmoreceptors, baroreceptors and cortical centers, impinge upon a common site, the magnocellular neuron, which sums these sig-

nals algebraically and responds by increasing or decreasing the elaboration of the effector hormone arginine vasopressin (AVP), which, in turn, modulates kidney function referable to restoration of water balance. The sensitivity and economy of this system is paralleled by another set of afferent-efferent relays involving thirst, which complements the antidiuretic response and provides a back-up capable of insuring survival of the organism should the AVP-renal circuit fail, as in the case of diabetes insipidus.

Although there is abundant information available about water processing, several physiologic and pathophysiologic questions remain unresolved. One such issue relates to the synergy between the renal medullary interstitium and the collecting duct in promoting antidiuresis. The increase in collecting-duct water permeability produced by ADH requires a gradient of medullary interstitial hypertonicity to effect water conservation by way of antidiuresis; and, as noted by Weitzman and Kleeman, the gradient of medullary interstitial hypertonicity is actually enhanced during sustained ADH release. In this connection, it is noteworthy that Morel and associates[4] have found that physiologic concentrations of ADH stimulate the production of cyclic adenosine monophosphate (cyclic AMP) in the water-impermeable, thick ascending limb of Henle. Therefore, one may speculate about the possibility that ADH might enhance salt absorption in this region of the nephron, thereby enriching solute accumulation by the medullary interstitium, and consequently enhancing the net effect of ADH-mediated increases in the water permeability of the collecting duct.

Weitzman and Kleeman stress correctly the need for recognizing that nonosmolar volume changes—specifically, more than a 5 percent reduction in plasma volume[5]—provide a physiologically appropriate stimulus for ADH release. In practical terms, this means that the diagnosis of the syndrome of inappropriate ADH production (SIADH) cannot be made with confidence in a patient in whom fluid volume is contracted, because in the latter circumstance failure to osmoregulate is the consequence of volume-mediated stimuli to ADH release overriding the tendency of hypotonicity to suppress ADH release.

Finally, the available information on thirst leaves unexplained the seeming paradox of hyponatremia occurring in alert, normovolemic patients with SIADH. As Weitzman and Kleeman point out in their review, a variety of stimuli related to volume, such as reduced cardiac output or vascular or extracellular fluid volume contraction, excite the sensation of thirst, possibly by way of the renin-angiotensin axis. Thus, there is a rational frame of reference for understanding why a patient with contracted fluid volume, or one with congestive heart failure, may continue to ingest water even in the face of dilutional hyponatremia. But why is thirst not suppressed in alert patients with SIADH resulting from ectopic ADH production, for example by a pulmonary neoplasm? One cannot argue that, in such a condition, there is a common stimulation of the thirst centers and the centers for ADH release, as might occur in a skull fracture. Likewise, if a patient with SIADH resulting from a pulmonary neoplasm is normovolemic, it is obvious that a factor or factors other than volume contraction stimulate thirst in the face of hyponatremia. When viewed in this context, one may ask whether SIADH involves not only inappropriate production of ADH but also an abnormality of thirst; or put differently, does SIADH involve both the water-acquiring and water-conserving limbs of the system for osmotic homeostasis?

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REFERENCES

1. Smith HW: From Fish to Philosopher: The Story of Our Internal Environment. Summit, NJ, CIBA Pharmaceutical, Inc. 1959

2. Verney EB: The antidiuretic hormone and the factors which determine its release. Proc R Soc Lond [Biol] 135:25-106, 1947

3. Robertson GL: Vasopressin in osmotic regulation in man. Ann. Rev. Med. 25:315-322, 1974

4. Imbert-Temboul M, Chabardès D, Montégut M, et al: Vasopressin-dependent adenylate cyclase activities in the rat kidney medulla: Evidence for two separate sites of action. Endocrinology 102:1254-1261, 1978

5. Dunn FL, Brennan TJ, Nelson AE, et al: The role of blood osmolality and volume in regulating vasopressin secretion in the rat. J Clin Invest 52:3212-3219, 1973

CASE REPORTS

Refer to: Bracis R, Seibers K, Julien RM: Meningitis caused by group II J following a dog bite. West J Med 131:438-440, Nov 1979

Meningitis Caused by Group II J Following a Dog Bite

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THE INCIDENCE of dog bites has been increasing in recent years.[1] While Pasteurella multocida is a well-known pathogen in such incidents, other organisms are also present in canine oral flora but their pathogenicity has not been well established.[2-4] One of these organisms was first isolated from a canine nasal swab in 1972.[4] It has since received the Center for Disease Control (CDC) alphanumeric designation group II J. We have recently seen a patient in whom meningitis following multiple dog bites developed and CDC group II J was cultured from the spinal fluid.

Report of a Case

A five-year-old girl was admitted to hospital because of fever, lethargy and headache. The patient had been well until three days before admission when a malamute dog bit her on the head and neck, and she sustained several lacerations. The patient's wounds had been cleaned in a local emergency department and she was treated with penicillin, 250 mg given four times a day. The girl vomited the first three doses of penicillin, but no subsequent vomiting occurred. On the day before the patient entered hospital she had a fever of 38.9°C (102°F), was lethargic, complained of frontal headache and stiffness of the neck, and stated that it hurt to open her mouth.

On initial physical examination, the patient was lethargic and appeared acutely ill. Temperature was 39.0°C (102.2°F), pulse was 128 per minute, respirations were 28 per minute, and blood pressure was 104/62 mm of mercury. Examination of the head showed multiple superficial scalp wounds with surrounding erythema, while ears, nose and mouth showed no abnormalities. Examination of the neck showed decreased range of motion and increased stiffness. No clinically significant adenopathy was noted. Lungs, heart and abdomen were normal. The Kernig sign was positive.

Laboratory studies at admission gave the following values: normal electrolytes, blood urea nitrogen and glucose as well as normal hemoglobin and hematocrit. Leukocytes numbered 19,700 per cu mm with 82 percent neutrophils, 3 percent bands, 8 percent lymphocytes and 7 percent monocytes. Platelet count was 400,000 per cu mm and erythrocyte sedimentation rate was 28 mm per hour. Spinal fluid showed 50 erythrocytes and 1,108 leukocytes (100 percent neutrophils) per cu mm; glucose was 65 and protein 58 mg per dl. The Gram stain showed no organisms.

Initial therapy included administration of nafcillin, 200 mg, penicillin, 200,000 units, and chloramphenicol, 100 mg per kg of body weight per day.

By the second hospital day the patient was afebrile. Skull x-ray studies showed no abnormalities. Gram stain of colonies cultured from cerebral spinal fluid (CSF) at 24 hours showed small, Gram-negative, bipolar staining rods. Blood cultures were negative. Administration of penicillin was increased to 250,000 units per kg of body weight per day.

The patient's status was unchanged on the third hospital day. Organisms cultured from CSF were tentatively identified as a Pasteurella species. Preliminary sensitivity testing showed that the organism was sensitive to penicillin; therefore, nafcillin and chloramphenicol therapy was discontinued. On the fourth day, physical examination showed a more active patient, with persistent headache and stiffness. An additional bacteriologic study determined that the organism was not a Pasteurella species. On the sixth day, the cul-

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ture was identified as CDC group II J. Clinically the patient was substantially improved. Repeat spinal tap was done on the eighth day, and these findings were noted: five erythrocytes and five leukocytes (20 percent neutrophils and 80 percent lymphocytes) per cu mm. Glucose was 51 and protein 13 mg per dl. On the 14th day, administration of penicillin was discontinued. Five months after discharge the patient was asymptomatic except for continuous drainage from a wound above the right ear. At exploration, a tract, 5 mm in diameter, was noted extending through the skull and exposing the dura. Computerized axial tomography (CAT) showed no evidence of a brain abscess.

Bacteriologic Studies

After overnight incubation (35°C, and under 3 percent carbon dioxide) the organism grew well on blood and chocolate agar but not on MacConkey agar. The initial Gram stain showed a pleomorphic, bipolar staining, Gram-negative rod ranging in length from 2 to 4 μ. Because of these characteristics, and the fact that catalase, oxidase and indole tests were positive, Pasteurella multocida was initially thought to be the responsible organism. However, a positive urease test and the lack of acid production from glucose made identification of P. multocida less likely. The culture was then identified by the CDC classification of miscellaneous Gram-negative bacteria as group II J.[5]

Initial disk susceptibility tests were done on Mueller-Hinton agar, and while the organism grew poorly, it appeared to be susceptible to penicillin. Group II J did not grow well in trypticase soy broth, Mueller-Hinton broth, brain-heart infusion or Columbia broth. A broth composed of one part Levinthal's medium (Prepared Media Lab, Tualatin, Oregon) and one part brain-heart infusion broth provided adequate growth for the organism.[6] Broth dilution susceptibility tests were done using that medium. The minimal inhibitory concentration (MIC) of penicillin was 0.016 units per ml and the minimal bactericidal concentration (MBC) was 0.031 units per ml. Chloramphenicol had a MIC of 0.2 μg per ml and a MBC of 1.6 μg per ml.

Discussion

Because of the rising incidence of dog bites, physicians should better acquaint themselves with canine flora, especially where it differs from that of humans. Dogs have a variety of unnamed species in their mouths. While some laboratories may identify them as Pasteurella-like, many of these isolates may actually fall into the CDC's alphanumeric classification.

In a recent survey of the oral and nasal flora of canines, group II J was found in 90 percent of the dogs tested. Other organisms found in more than 50 percent of the animals included: EF-4, Pastuerella multocida and Staphylococcus aureus.[4] To date, less than 100 isolates of group II J have been reported to the CDC (Robert Weaver, personal communication). An organism classified as Unidentified Species No. 5 was found less frequently.

Butler and co-workers have reported a series of 17 patients with bacteremia from an unidentified Gram-negative rod.[7] Most had suffered dog bites before their illnesses and four of these patients also had meningitis. Almost all the patients had a significant underlying disease. This unidentified Gram-negative rod had the same characteristics as Unidentified Species No. 5, noted in the survey of canine flora done by Bailie and colleagues.[4]

If group II J is so common in canine mouth flora, one may ask why more infections have not already been seen with this organism. It is possible that the organism has been either identified by microbiology laboratories as a Pasteurella species or has been considered a contaminant. While group II J grew well on blood and chocolate agar, it did not grow on media routinely used for Kirby-Bauer agar diffusion susceptibility. The fact that group II J is exquisitely sensitive to penicillin may mean that other unrecognized cases may have been treated by serendipity. Group II J may be less virulent than other organisms found in canine mouth flora or, perhaps, a compromised host is necessary for it to be pathogenic.

Summary

Infections secondary to relatively unusual pathogens, and resulting from animal bites appear to be on the rise. Awareness of these organisms by both microbiology laboratories and clinicians may lead to their increased recognition and identification.

REFERENCES

1. Animal Bites in the United States. CDC Veterinary Public Health Notes (November). US Dept of Health, Education and Welfare, Center for Disease Control, Atlanta, Georgia, 1975

2. Holloway WJ, Scott EG, Adams YB: Pasteurella multocida infection in man, report of 21 cases. Am J Clin Pathol 51:705-708, 1969

3. Saphir DA, Carter GR: Gingival flora of the dog with special references to bacteria associated with bites. J Clin Microbiol 3: 344-349, 1976

4. Bailie WE, Stowe EC, Schmitt AM: Aerobic bacterial flora of oral and nasal fluids of canines with reference to bacteria associated with bites. J Clin Microbiol 7:221-223, 1978

5. Tatum HW, Ewing WH, Weaver RE: Miscellaneous Gram-negative bacteria, *In* Lennette EH, Spaulding EH, Truant JP (Eds): Manual of Clinical Microbiology, 2nd Ed. Washington, DC, American Society for Microbiology, 1974, pp 270-294

6. Gordon RC, Thompson TR, Stevens LI, et al: In Vitro susceptibility of Haemophilus influenza to eight antibiotics. Antimicrob Ag Chemother 6:114-115, 1974

7. Butler TB, Weaver RE, Venkata Ramani TK, et al: Unidentified Gram-negative rod infection. Ann Intern Med 86:1-5, 1977

Refer to: Skory L, Shearn MA: Psoriatic arthritis induced by varicella. West J Med 131:440-441, Nov 1979

Psoriatic Arthritis Induced by Varicella

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THERE HAS BEEN increasing evidence in recent years to implicate viruses as etiologic factors in the pathogenesis of arthritic disorders.[1] Such entities accompanying infection with mumps, rubella and hepatitis B are well recognized, but a variety of other viruses such as rubeola, smallpox and the arboviruses may also induce articular disease.[2] The pattern of joint disease produced by viral infection varies. Often, both small and weight-bearing joints are affected symmetrically, as in rubella arthritis.[2]

At the University of California Medical Center in San Francisco, we recently saw a patient with psoriasis and no previous arthritis in whom psoriatic arthritis involving the distal interphalangeal (DIP) joints developed after a varicella infection. With resolution of the infection, the arthritis cleared completely and the psoriasis was considerably improved.

Report of a Case

A 22-year-old woman had a three-year history of psoriasis, which had flared severely four months before the present episode. Joint disease had not previously been noted. Two weeks before admission to hospital, typical lesions of varicella developed; the patient said she had not had chickenpox in childhood. A week before admission, she noted psoriatic lesions at the site of each vesicle. At the same time, she had throbbing pain in all the DIP joints, associated with intense redness and swelling.

Physical findings were confined to the skin, which bore hundreds of guttate plaques, and to the hands. The nails showed onycholysis and Beau lines consistent with a previous episode of severe psoriasis. All DIP joints of the hands were tender, swollen and erythematous. Findings on analysis of urine, hemogram and erythrocyte sedimentation rate, liver enzyme, uric acid, VDRL, antinuclear antibody and rheumatoid factor studies were all within normal limits. HLA (histocompatibility antigen) typing was not done, and x-ray films of the hands showed no bony abnormalities.

Indomethacin, administered in a dosage of 25 mg three times a day, provided symptomatic relief; after nine days, the psoriatic arthritis had cleared completely with resolution of the varicella.

Arthritis had not recurred after 11 months, when a follow-up examination was done.

Comment

Arthropathy is a frequent manifestation of many common viral infections. Arthritis accompanying varicella is rare; in the few cases reported, monoarticular, large joint involvement occurred coincident with the development of the skin lesions.[3,4] In our patient, the anatomic location and temporal sequence differed. The arthritis occurred a week after viral infection, and articular involvement was confined to the DIP joints, which is typical of psoriatic arthritis.

In psoriasis, the joints may be affected in a variety of clinical patterns that include oligoarthritis, symmetric polyarthritis, ankylosing spondylitis, arthritis mutilans and classic psoriatic arthritis with predominant or exclusive involvement of the DIP joints.[5,6]

The classic form of psoriatic arthritis developed in our patient. The DIP joints, which appear to be predisposed to arthritis in some psoriatic patients, were affected following varicella. Although the psoriatic arthritis and the varicella infection might have been independent events, the temporal relationship and rapid resolution of arthritis after clearing of varicella suggest that the virus was an

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important factor in the pathogenesis of the articular disease.

Summary

In a young woman with psoriasis and no previous arthritis, varicella was associated with arthritis affecting the DIP joints in the pattern of classic psoriatic arthritis. The rapid clearing of the arthritis with resolution of the varicella suggests that the virus may have triggered the arthritis in susceptible joints.

REFERENCES

1. Bennett JC: The infectious etiology of rheumatoid arthritis. Arthritis Rheum 21:531-538, Jun 1978
2. Arthritis caused by viruses—Medical Staff Conference, University of California, San Francisco. Calif Med 119:38-44, Sep 1973
3. Mulhern LM, Friday GA, Perri JA: Arthritis complicating varicella infection. Pediatrics 48:827-829, Nov 1971
4. Ward JR, Bishop B: Varicella arthritis. JAMA 212:1954-1956, Jun 1970
5. Leonard DG, O'Duffy JD, Rogers RS: Prospective analysis of psoriatic arthritis in patients hospitalized for psoriasis. Mayo Clin Proc 53:511-518, Aug 1978
6. Moll JMH, Wright V: Psoriatic arthritis. Semin Arthritis Rheum 3:55-78, 1973

Refer to: Warren SE, Boice JB, Bloor C, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. West J Med 131:441-447, Nov 1979

The Athletic Heart Revisited

Sudden Death of a 28-Year-Old Athlete

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IN THE PAST *organic heart disease* was often the diagnosis when an asymptomatic, trained athlete presented with electrocardiographic evidence of left ventricular hypertrophy and a large heart shown on x-ray studies. In recent years, however, the diagnosis is more likely to be *athletic heart syndrome*.[1-5] This increasingly popular diagnosis is usually applied to young athletes capable of championship performance who are found to have evidence of cardiac hypertrophy and enlargement, a slow resting heart rate, systolic ejection murmur and, occasionally, a variety of arrhythmias and conduction disturbances.[1] This condition has been thought adaptive, benign and reversible, and restrictions on physical activity were not thought to be indicated.[6,7] Nevertheless, occasional reports of sudden death in marathon runners with patent coronary arteries[8,9] and the knowledge that only a history of athletic prowess deters a diagnosis of cardiomyopathy in a patient with unexplained cardiac enlargement, calls into question the presumed benign nature of this condition. Moreover, the adaptive response of a normal heart to isotonic and isometric exercise differs, and it is not known under what circumstances (if any) the response may become pathologic.

Just as a patient with the athletic heart syndrome is asymptomatic at diagnosis, so too may be persons from a kindred destined to manifest familial cardiomyopathy, who often have a subsequent malignant course characterized by congestive heart failure or sudden death.[10-12] If these patients were initially capable of competitive physical exercise, it is possible that a spurious diagnosis of athletic heart syndrome would be made and the person encouraged to pursue limitless physical exertion, perhaps at some hazard.

In this paper we report the case of a young national champion tennis player who carried the diagnosis of athletic heart syndrome for six years following a complete cardiac evaluation in 1972. In this woman and several members of her family, all athletically active, concentric left ventricular hypertrophy was shown by echocardiography. The woman collapsed while playing tennis and died within 24 hours. On autopsy there was evidence of acute myocardial infarction, patent coronary arteries and diffuse cardiomyopathy.

Reports of Cases

CASE 1. At the time of initial evaluation in 1972, the then 23-year-old patient had a negative past medical history and had participated competitively in a variety of sports including tennis, field hockey, basketball, volleyball, swimming and track. Her best time in the 100 yard dash was 11.9 seconds, in the 440 yard dash 61.1 seconds and in the two mile run 12 minutes 36 seconds. She was a recent singles runner-up in the All-Navy Tennis Tournament. The patient

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desired to be a naval aviator and was referred to the Cardiology Department, Naval Regional Medical Center, San Diego, California, after a routine x-ray study of the chest and an electrocardiogram showed left ventricular prominence and hypertrophy (Figures 1 and 2A).

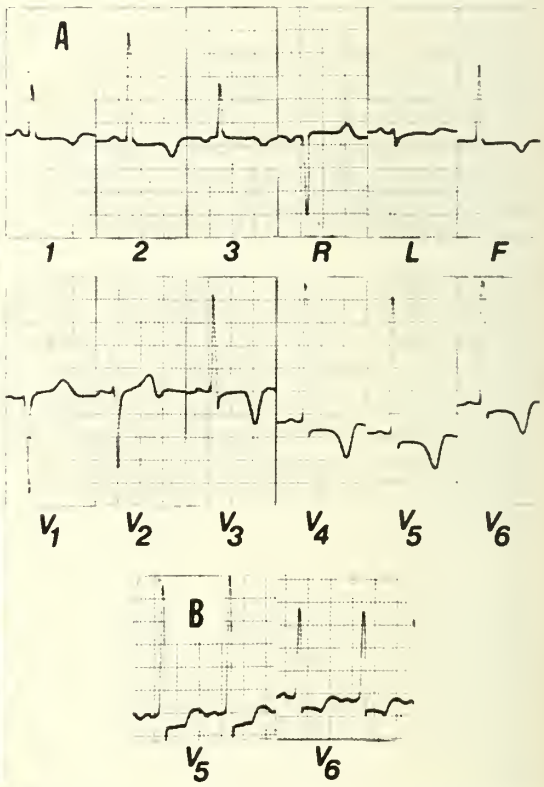
Physical examination disclosed a resting pulse of 50, blood pressure 120/75/55 mm of mercury, a grade I/VI systolic ejection murmur at the left sternal border, and a third heart sound. A treadmill test done according to the protocol by Bruce[13] was stopped after 18 minutes because the patient became fatigued, a maximum heart rate of 200 beats per minute having been achieved. No chest pain occurred; the postexercise tracing is shown in Figure 2B. An echocardiogram (Figure 3 and Table 1) disclosed increased thickness of the ventricular septum and posterior wall of the left ventricle with a normal ratio and normal left ventricular function. Findings at cardiac catheterization included a symmetrically thickened ventricle, mildly elevated right and left ventricular end-diastolic pressures (11 and 17 mm of mercury), an ejection fraction of 83 percent, normal coronary arteries, and no valvular disease or gradients. Hypertrophic subaortic stenosis (IHSS) was excluded by postpremature ventricular contraction pressure changes and isoproterenol infusion. A diagnosis of athletic heart syndrome was made.

Several months later the patient embarked on a professional tennis career, playing competitively until 1976. At that time, she experienced the onset of frequent 15- to 30-minute episodes of crushing substernal chest pains associated with shortness of breath, nausea and diaphoresis, occurring at rest. The frequency of discomfort remained stable at every other day, and the patient continued to play tennis and jog 1 to 3 miles a day.

In February 1978 (at age 28), the patient collapsed shortly after beginning a tennis match; she was resuscitated, but died within 24 hours. Her brief time in hospital was complicated by clinical, electrocardiographic and enzymatic evidence of acute anteroseptal myocardial infarction, adult respiratory distress syndrome and malignant ventricular arrhythmias.

Autopsy Findings

At necropsy, the heart weighed 500 grams and showed left ventricular prominence. The atria were mildly dilated. Transverse sections of the heart showed bilateral, diffuse, concentric hypertrophy



Figures 1 and 2.—Roentgenogram of the chest and electrocardiogram in an outstanding 23-year-old female athlete showing left ventricular hypertrophy. Item B in Figure 2 is the postexercise electrocardiogram.

which was more pronounced in the left ventricle. Although the right ventricle had a normal chamber size, the pronounced left ventricular hypertrophy significantly reduced left ventricular chamber size. The anterior, posterior and lateral walls of the left ventricle and interventricular septum were equally involved, averaging about 2.8 cm in thickness (Figure 4). The interventricular septum/posterior wall thickness ratio of the left ventricle was 1.0. At its point of maximum thickness the right ventricular free wall measured 0.9 cm. The coronary arteries and valves were normal.

At the left ventricular apex extensive regions of circumferential subendocardial infarct were noted. More cephalad, there were multifocal infarcts involving all regions of the ventricular wall, predominantly in the inner half. Several regions of old infarct were present in the posterior apical wall of the left ventricle.

Histologically, the zones of gross infarct showed characteristic changes including fiber disruption and cellular infiltrate consistent with an infarct of 24 to 48 hours duration. Sections of the coronary arteries were normal (Figures 5 and 6). Other myocardial lesions comprised diffuse interstitial broad band fibrosis and myocardial fiber hypertrophy which were present in sections from the walls of both ventricles. No changes of amyloidosis, sarcoidosis, storage disease or rheumatic heart disease were present.

Figure 3.—Echocardiogram in a 23-year-old female athlete showing concentric hypertrophy with posterior wall (PW) thickness of 14 mm in diastole. Septal measurements were determined from other portions of the echocardiogam.

Case histories of family members are given below.

Case 2. The father of the patient is a 60-year-old former semiprofessional athlete who was active in track, basketball, swimming and tennis. An excellent tennis player all his life, in recent years he has confined tennis to doubles because of eye surgical procedures. He has had no symptoms of cardiovascular disease, but gives a history of having "a large heart" all his life. During evaluation in 1972, he was found to have a resting pulse of 50, blood pressure 175/90/90 mm of mercury and a grade II/VI systolic ejection murmur at the left sternal border. An x-ray study of the chest showed left ventricular prominence and an electrocardiogram indicated left ventricular hypertrophy (Figures 7 and 8A). He exercised seven minutes on the treadmill[13] and achieved a maximum heart rate of 135 beats per minute before the test was stopped due to shortness of breath. The postexercise tracing appears in Figure 8B. Echocardiographic results appear in Table 1.

Case 3. The 33-year-old brother of the patient in the index case is an aviator with an outstanding athletic record. In 1972 an x-ray study of the chest and an electrocardiogram showed left ventricular prominence. During evaluation in 1972 he completed 18 minutes on the treadmill without chest pain, arrhythmia, or significant postexercise ST segment changes developing. Echocardiographic results appear in Table 1.

Case 4. The 31-year-old married sister of

TABLE 1.—*Echocardiographic Profile of an Athletic Family*

	EDD	*ESD*	*SV*	*EF*	*Vcf*	*Δd/d*	*S&PWT*
Normal	35-53			59-75	1-1.5	32-39	8-11
Case 1 (1972) Index case	47	28	82	79	1.26	40	14
Case 2 (1978) Father	42	24	60	81	1.20	43	14
Case 3 (1978) Brother	52	32	108	77	1.75	58	13
Case 4 (1978) Sister	43	26	62	78	1.13	40	9
Case 5 (1978) Mother	41	24	55	80	1.12	41	9

EDD = end-diastolic dimension (in millimeters)
ESD = end-systolic dimension (in millimeters)
SV = stroke volume (in cubic centimeters)
EF = ejection fraction (in percent) (determined by cubing the short diameter)
Vcf = mean velocity of circumferential fiber shortening (in circumferences per second)
Δd/d = fractional shortening (in percent)
S&PWT = septal and posterior wall thickness at end diastole (in millimeters)

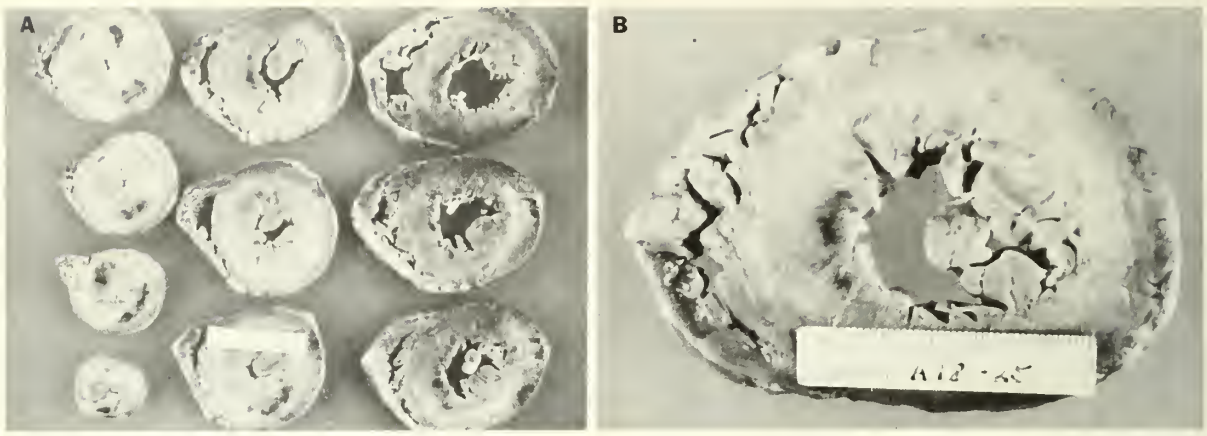


Figure 4.—Concentric hypertrophy, myocardial fibrosis and acute and old myocardial infarctions in a 28-year-old female champion athlete. Darkened areas show fresh subendocardial infarction.

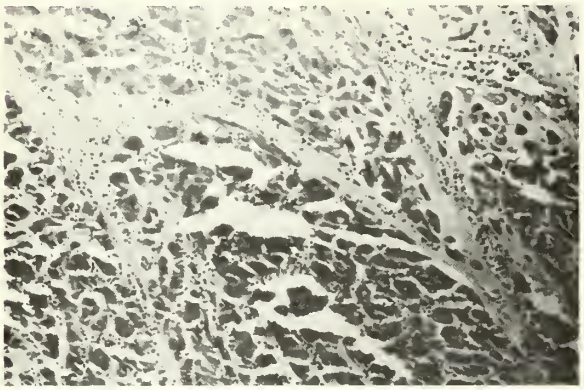


Figure 5.—Microscopic section of anterior left ventricular myocardium using hematoxylin-eosin stain. Entire field shows infarction with an interstitial leukocytic infiltrate.

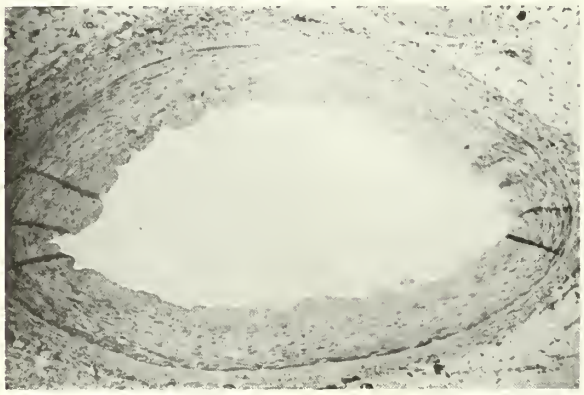


Figure 6.—Normal left anterior descending coronary artery representative of remaining coronary system.

the patient was an outstanding athlete in high school, but subsequently injured her knee and retired from competitive sports. An x-ray study of the chest, electrocardiogram and echocardiogram are normal. Echocardiographic results appear in Table 1.

CASE 5. The 62-year-old mother has no history of competitive athletics or heart disease. Physical examination, electrocardiogram and x-ray study of the chest showed no abnormalities. Echocardiographic results appear in Table 1.

Discussion

The myocardial response to exercise has been studied extensively.[14-19] While the resting left ventricular function of a sedentary person is comparable to that of a trained athlete,[19] differences emerge during exercise. Increased oxygen needs, hence increased cardiac output, can be supplied by increases in heart rate, stroke volume, or both of these. In an untrained person this requirement is met chiefly by the heart rate increasing, while in an athlete both heart rate and stroke volume are utilized.[15,16] The latter may be due partially to increased cardiac end-diastolic volume.[17] Moreover, in an athlete there is an enhanced ability to extract oxygen peripherally.[18]

Both chronic isometric exercise and isotonic exercise result in increased left ventricular mass, while isotonics also produce increased ventricular volume.[3,14,22] In an athlete these changes are brought about by an enlargement of myocardial fiber size rather than number, and occur without accompanying fibrosis (as in the volume stress of regurgitant valvular or primary myocardial disease; see Table 2).[20-22] There has been doubt as to the universal adequacy of capillary flow to match an enlarging myocardial mass,[23] such that stressed muscle fibers might ultimately suffer nutritional deficiency and hypoxia,[24] or perhaps be prone to failure. In fact, elevated end-diastolic pressures have been recorded in young athletes,[7]

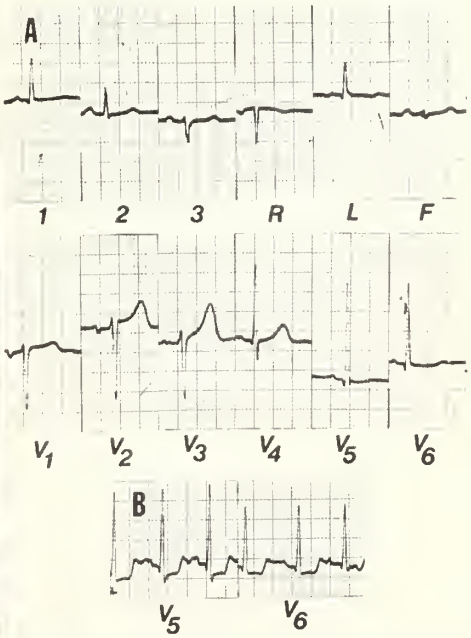
as well as sudden death with patent coronary vessels.[8,9]

Fortunately, from a clinical standpoint, the heart has never been shown to outgrow its own blood supply, with the possible exception of cases of congenital single coronary artery.[25] Could familial cardiomyopathy be a second example, at least in the presence of exercise? This may have been the case in our patient.

The patient in the index case reported in this paper presented without symptoms in 1972, and evidence of left ventricular hypertrophy was noted. Secondary causes of ventricular hypertrophy such as hypertensive cardiovascular disease, aortic stenosis and idiopathic hypertrophic subaortic stenosis were excluded at catheterization and autopsy; nor were secondary causes of diffuse myocardial disease found to be present. A diagnosis of familial cardiomyopathy was entertained[10-12] in light of the presence of several similarly affected family members, but this diagnosis was not established because of several considerations.

First, a review of 11 families with 47 members showing familial cardiomyopathy disclosed a mean age at diagnosis of 24 years, with most cases showing symptoms by the fifth decade.[10] Our patient's asymptomatic father in his 60's militated against such a process. Second, while familial cardiomyopathy may be asymptomatic at discovery,[10] enhanced performance is not seen.[11,12] To our knowledge, in fact, there are no well-documented reports in the literature showing championship performance in a patient destined to die because of familial cardiomyopathy. Third, the criteria of Gott and coworkers[1] for the diagnosis of the athletic heart syndrome were fulfilled: namely, a history of athletic endurance, biventricular enlargement, systolic ejection murmur, third heart sound, resting sinus bradycardia and increased indices of cardiac function.

In retrospect, we believe that the patient in the index case probably had a variant of familial cardiomyopathy[26] with some features of the athletic heart syndrome. Her principal forms of exercise were isotonic. Yet, her echocardiogram in 1972 showed left ventricular hypertrophy without dilatation as did her father's and brother's echocardiograms in 1978. Often there is echocardiographic evidence of both left ventricular hypertrophy and dilatation in an endurance-trained athlete.[18,29] Her resting electrocardiogram showed repolarization changes consistent with left ventricular strain (pressure or systolic overload). In contrast, the usual resting electrocardiogram in a trained athlete shows early repolarization with or without tall T-waves (volume or diastolic overload).[27] Following treadmill exercise testing there was ST segment flattening and depression of greater than 2 mm consistent with an *"ischemic*



Figures 7 and 8.—Roentgenogram of the chest and electrocardiogram showing left ventricular hypertrophy in a 60-year-old former champion athlete (case 2). Item B in Figure 8 is the postexercise electrocardiogam.

response" in both the patient (case 1) and her father (case 2). Such postexercise electrocardiographic changes are rarely seen in the athletic heart syndrome.[22]

Postmortem examination in the index case showed striking evidence of left ventricular hypertrophy which presumably progressed over the preceding years. The echocardiogram in 1972 showed septal and posterior wall thickness of 14 mm during diastole in comparison to 28 mm at necropsy in 1978. Even if the heart had arrested at end-systole, there had been significant progression of hypertrophy. In addition to hypertrophy there was evidence of old and new myocardial infarcts in the presence of patent coronary arteries. Clearly, either myocardial perfusion was inadequate to meet the demands of the hypertrophied heart or myocardial flow was redistributed, making the subendocardial zones more vulnerable to ischemic damage.

Because most reviews and case reports of the athletic heart syndrome fail to provide long follow-up or to examine other family members, it is possible that some athletes so labelled do, in fact, have underlying heart disease that will become manifest at a future date. For any individual case it may be difficult to differentiate cardiomyopathy from the athletic heart syndrome. In addition to cardiac enlargement and hypertrophy, ventricular gallop and systolic ejection murmur, both conditions may show a variety of arrhythmias, conduction disturbance and repolarization changes.[6,10,27]

Sudden death may be the first clinical sign of cardiomyopathy[28] and, therefore, it is obvious that a correct diagnosis in a young patient with an enlarged, hypertrophied heart is essential. To this end, we believe that in addition to the diagnostic maneuvers described above, a complete history with examination of family members should be carried out. If cardiomegaly on x-ray films of the chest, left ventricular hypertrophy on electrocardiograms and measurably increased wall thickness on echocardiograms are found in family members (especially if not athletic), great caution should be exercised before a diagnosis of athletic heart syndrome is applied. Even if, as in our case, affected family members have been athletic, due to the highly variable clinical expression of familial cardiomyopathy[10] the patient and relatives should receive close follow-up.

Summary

A young female athlete capable of championship performance presented in 1972 with left ventricular prominence, left ventricular hypertrophy with strain and concentric left ventricular hypertrophy on x-ray studies of the chest, electrocardiogram and echocardiogram, respectively. Several family members, including her asymptomatic 60-year-old father, were also found to possess both athletic histories and large hearts. In view of the history and asymptomatic status of older family members, a diagnosis of athletic heart syndrome was made. Six years later the patient suffered a cardiac arrest during exercise, and an autopsy showed evidence compatible with familial cardiomyopathy. It is concluded that patients with familial cardiomyopathy may be capable of competitive physical endurance initially and that physicians should defer a diagnosis of athletic heart syndrome in athletic patients with large hearts until proper diagnostic tests and family studies are done.

REFERENCES

1. Gott PR, Rosselle HA, Crampton RS: The athletic heart syndrome—Five-year cardiac evaluation of a champion athlete. Arch Intern Med 122:340-344, 1968

2. Grande F, Taylor HL: Adaptive changes in the heart, ves-

TABLE 2.—*Pathologic Spectrum of Myocardial Hypertrophy*[20-22]

	Normal Sedentary	*Normal Athlete*	*Pathologic Concentric (Early Pressure Loads)*	*Pathologic Eccentric (Valvular Regurgitation, Myocardial Disease Excluding IHSS)*
Heart weight	Normal	↑ but<500 grams	≥500 grams	≥500 grams
Number of fibers	Normal	Normal	Normal	↓
Fiber size	Normal	↑	↑	↑↑
Fibrosis	Absent	Absent	Generally absent	Present
Ventricular cavity size	Normal	Normal or ↑; ↓ in systole	Normal or ↓	↑

↑ increased ↓ decreased ↑↑ greatly increased IHSS = hypertrophic subaortic stenosis

sels, and patterns of control under chronically high loads. *In* Hamilton WF, Dow P (Eds): Handbook of Physiology: Circulation, Vol III. Washington, DC, 1965, Am Physiol Soc, pp 2615-2677

3. Roeske WR, O'Rourke RA, Klein A, et al: Noninvasive evaluation of ventricular hypertrophy in professional athletes. Circulation 53:286-292, 1976

4. Morehouse LE, Miller AT Jr: Physiology of Exercise, 5th Ed. St. Louis, The C V Mosby Co, 1967, pp 93, 286, 287

5. Pyorala J, Kyronseppa H: Cardiovascular studies on former endurance athletes, *In* Karvonen MJ, Barty AJ (Eds): Physical Activity and the Heart. Springfield, IL, Charles C Thomas, 1967, pp 301-310

6. Lichtman J, O'Rourke RA, Klein A, et al: Electrocardiogram of the athlete. Arch Intern Med 132:763-770, 1973

7. Marcano BA, Moss AJ: Spurious heart disease in athletic children. J Pediatr 72:664-668, 1968

8. Green LH, Cohen SI, Kurland G: Fatal myocardial infarction in marathon racing. Ann Intern Med 84:704, 1976

9. Lollgen H, Just HJ, Mathes P: Myokardinfarkt bei einem Hochleistungs-Sportler mit normalen Koronarterien. Dtsch Med Woch 98:620, 1973

10. Kariv I, Kreisler B, Sherf L, et al: Familial cardiomyopathy—A review of 11 families. Am J Cardiol 28:693-706, 1971

11. Evans W: Familial cardiomyopathy. Br Ht J 2:68-82, 1949

12. Boyd DL, Mishkin ME, Feigenbaum H, et al: Three families with familial cardiomyopathy. Ann Intern Med 63:386-401, 1965

13. Doan AE, Peterson DR, Blackman JR, et al: Myocardial ischemia after maximal exercise in healthy man. Am Heart J 69: 11:21 1965

14. Wenger NK, Gilbert CA: Athletes heart, *In* Hurst JW (Ed): The Heart. New York, McGraw-Hill Book Co, 1978, pp 1706-1709

15. Rushmer RF, Smith O: Cardiac control. Physiol Rev 39: 41, 1959

16. Rushmer RF, Smith O, Franklin D: Mechanism of cardiac control in exercise. Circ Res 7:602 1959

17. Sarnoff ST, Mitchell JH: The control of the function of the heart, *In* Hamilton WF (Ed): Handbook of Physiology: Circulation, Vol 1. Washington, DC, American Physiological Society, 1962, p 525

18. Bevegard S, Holmgren A, Jonsson B: Circulatory studies in well-trained athletes at rest and during heavy exercise, with special reference to stroke volume and the influence of body position. Acta Physiol Scand 57:26-50, 1963

19. Gilbert CA, Nutter DO, Felner JM, et al: Echocardiographic study of cardiac dimensions and function in the endurance-trained athlete. Am J Cardiol 40:528-533, 1977

20. Badeer HS: Biological significance of cardiac hypertrophy (Editorial). Am J Cardiol 14:133-138, 1964

21. Allen WD, Goldberg SJ, Sahn DJ, et al: A quantitative echocardiographic study of champion childhood swimmers. Circulation 55:142-145, 1977

22. Raskoff WJ, Goldman S, Cohn K: The athletic heart. JAMA 236:158-162, 1976

23. Honig CR, Bourdeau-Martin J: Extravascular component of oxygen transport in hypertrophied hearts with special reference to oxygen therapy. Circ Res 35 (Suppl II):II-97, 1974

24. Linzbach AJ: Heart failure from the point of view of quantitative anatomy. Am J Cardiol 5:370, 1960

25. Warren SE, Alpert JS, Vieweg WVR, et al: Normal single coronary artery and myocardial infarction. Chest 72:540-543, 1977

26. Perloff JK: The cardiomyopathies—Current perspectives. Circulation 44:942-949, 1971

27. Hanne-Paparo N, Drory Y, Schoenfeld Y, et al: Common ECG changes in athletes. Cardiology 61:267-278, 1976

28. Maron BJ, Roberts WC, Edwards JE, et al: Sudden death in patients with hypertrophic cardiomyopathy: Characterization of 26 patients without functional limitation. Am J Cardiol 41:803-810, 1978

29. DeMaria AN, Neumann BS, Garrett L, et al: Alterations in ventricular mass and performance induced by exercise training in man evaluated by echocardiography. Circulation 57:237-243, 1978

Clinical Depression and Suicide

THERE EXISTS a powerful clinical bias not to understand depression as an illness, but rather to explain it away. A recent study of completed suicides makes two striking and uncomfortable observations: . . . the vast majority of these patients were under the recent care of a physician, and . . . a review of their records showed that clinicians had documented sufficient signs and symptoms to make a diagnosis of clinical depression . . . without having done so.

—HENRY R. BLEIER, MD, *Philadelphia*

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Irish Spring Soap

To the Editor: I am writing regarding a possible new effect of Irish Spring soap. I have frequently seen patients with dry erythematous and pruritic skin from the use of this strong detergent soap. However, today I saw a patient with a prominent miliaral rash on the face, neck, upper arms, upper back and upper chest. By a thorough history we ruled out other possible inciting factors.

I think it is a certainty that this miliaral rash was caused by the Irish Spring and this should be added to the list of negative skin effects of this product.

ED SARGENT, MD
Student Health Center
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Primary Hypertension—A Disease Entity?

To the Editor: The article by Drs. Rudd and Morton in the September issue presented an excellent review of problems associated with treatment of hypertension [Nontraditional Problems of Antihypertensive Management]. However, the authors seem to take for granted that primary hypertension is a well-defined disease entity.

If such an entity requires such a complicated lengthy treatment plan, there must be more involved than just levels of blood pressure. Can they really define or classify this entity with pathologic correlation, varieties of natural course, etiologic possibilities and so forth, as in more documented diseases such as types of arteritis—Wegener granuloma, for instance?

In the 1966 edition of *Controversies in Internal Medicine,* Drs. Goldring and Chasis concluded (after 30 years' research) that treatment of hypertension was not successful. But they did not think that treatment should be the real issue. They were concerned about the increasing emphasis in the literature on treating primary (then essential) hypertension with a corresponding decrease in studies on causes, pathologic findings and natural course; in other words, what is the real disease of which elevated blood pressure may be only a secondary or concomitant manifestation? In particular they were bothered by lack of knowledge about the relationship of hypertension to arterial disease, and disturbed that arterial disease progressed unabated in hypertensives whose blood pressure was reduced to normal by sympathectomy.

If we do not know any more about this now than in 1966 maybe, just maybe, primary hypertension is not really a disease entity. Perhaps there is a need to publish a few case reports.

JAMES W. KASCH, MD
Oakland, California

Of Decibels, 'Highs' and Privacy

To the Editor: Over in Iran, the Ayatollah Khomeini has banned all music, calling it the opiate of the masses. Here, in the land of the free and the home of inviolate human rights, we put this down as a despotic act of a senile dictator.

And yet, recalling the sights and sounds of the summer past, I have an uneasy feeling that the Ayatollah may be at least partly right. I remember that entranced faraway look in the eyes of the lad as he *tooled* slowly down the middle of our residential street, his radio tuned to top decibel. And I cannot forget how the young folks next door sent out throbbing, thumping, earsplitting beats through every open window to every unfortunate passerby.

Society is becoming aware of the physical dangers of noise, and is trying to abate noise pullution. In this lumbermill town, noise—loud

noise—is an accepted occupational hazard for the workmen. Noise dampening efforts are made, workers are encouraged to wear earplugs. But the saying is that when a millworker retires he is given not a watch but a gold-plated hearing aid. Out on our lake, motorboats are required to keep the noise of their exhausts below a certain level and underwater mufflers are mandatory.

But so far no legislator has dared suggest that mufflers be put on radios or decibel governors on stereos, even though the hearing acuity of future generations is in jeopardy. My audiologist friend suggests, half seriously, that by the year 2000 infants will be born with a hearing aid in place.

Everyone agrees we have a problem but we lack consensus on a solution. A first step might be to search for a cause of this phenomenon. A psychiatrist at the University of Chicago suggests our narcissistic younger generation turns up the volume to attract attention, the "Hey, look me over" syndrome. Another research worker maintains that the monotonous, repetitious sounds allow youths to block out the world of reality, while achieving their personal *high*. A less scholarly observation, undoubtedly made by a parent of a teenager, is that this hard-rock racket is simply an angry blast at the Establishment.

Whatever the explanation, the fact remains that these loud and pulsating sounds are an invasion of a person's privacy, as well as a cacophonous insult to his ear drums. Is there any hope for relief? The Ayatollah Khomeini's total prohibition would not work here. What we need is a forceful, grass-roots educational program.

Otolaryngologists of America, rise up in protest! Let your voices be heard. Mothers of America, make war on noise, lest universal deafness be the fate of future generations.

E. R. W. FOX, MD
Special Editor for Idaho
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Clonidine Withdrawal—Fact or Fiction?

To the Editor: The medical literature is unfortunately clouded by a maze of poorly defined terms to describe a syndrome occurring in some patients when antihypertension medication is abruptly stopped; these include discontinuation syndrome, acute posttreatment syndrome, acute withdrawal syndrome and rebound hypertension.

In a case report on clonidine withdrawal by Mate and his colleagues in the July issue (Mate TP, Swerdlin AHR, Stone RA, et al: Clonidine hydrochloride withdrawal complicating bilateral nephrectomy. West J Med 131:59-62, Jul 1979) several false and misleading statements are made concerning this syndrome. The authors attempt to incriminate clonidine withdrawal as the cause of "rebound hypertension." In the first place, the posttreatment blood pressures (250-270/100-120 mm of mercury) do not indicate any significant rebound over that of the pretreatment blood pressures (190-200/110-120 mm of mercury). Second, the authors state that "neither propranolol nor minoxidil withdrawal has been associated with a rebound phenomenon." The withdrawal syndrome is not unique to clonidine and has been reported to occur with bethanidine,[1] methyldopa[2-5] and propranolol.[6,7] Third, acute cessation of combination drugs especially a centrally acting antihypertensive in patients receiving propranolol may produce worse symptoms of blood pressure elevations than single agents alone due to uninhibited stimulation of vasoconstrictor alpha receptors during beta blockage.[8,9] The authors provide evidence that extreme levels of catecholamines appear to be the sole pressor mechanism responsible for the sustained hypertension. However, other studies have shown no excessive rise in catecholamines upon acute discontinuation of clonidine.[10,11]

It is interesting to note that abrupt cessation of clonidine (0.4 mg given orally twice a day) three days after its reinstitution in this patient did not result in another "rebound phenomenon." This is consistent with recent studies,[11,12] suggesting that doses of clonidine less than 1.2 mg per day did not result in overshoot blood pressure or symptoms of sympathetic overactivity. However, it could just as easily be interpreted that the combination of propranolol and clonidine or propranolol alone was the cause of the withdrawal syndrome in this patient. This case only adds more confusion to a poorly defined syndrome. Interchangeable use of terms such as rebound hyptertension and withdrawal syndrome should be avoided and an attempt made to distinguish between overshoot hypertension, return to pretreatment blood pressure, and sympathetic overactivity with or without hypertension. I do not believe it is justified in view of the above facts to implicate clonidine as the cause of this withdrawal syndrome. This case might just as easily

have been titled "Propranolol Withdrawal Complicating Bilateral Nephrectomy."

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REFERENCES

1. Goldberg AD, Raftery EB, Wilkinson P: Blood pressure and heart rate and withdrawal of antihypertensive drugs. Br Med J 1(6071):1243-1246, May 14, 1977

2. Horwitz D, Pettinger WA, Orvis H, et al: Effects of methyldopa in fifty hypertensive patients. Clin Pharmacol Ther 8:224-234, Mar-Apr 1967

3. Frewin DB, Penhall RK: Rebound hypertension after sudden discontinuation of methyldopa therapy. Med J Aust 1(18):659, Apr 30, 1977

4. Burden AC, Alexander CP: Rebound hypertension after acute methyldopa withdrawal. Br Med J 1(6017):1056-1057, May 1, 1976

5. Scott JN, McDevitt DG: Rebound hypertension after acute methyldopa withdrawal (Letter). Br Med J 2(6031):367, Aug 7, 1976

6. O'Brien ET, MacKinnon J: Propranolol and polythiazide in treatment of hypertension. Br Heart J 34:1042-1044, Oct 1972

7. Miller RR, Olson HG, Amsterdam EA, et al: Propranolol-withdrawal rebound phenomenon—Exacerbation of coronary events after abrupt cessation of antianginal therapy. N Engl J Med 293: 416-418, Aug 28, 1975

8. Chrysant SG, Whitsett TL: Withdrawal of antihypertensive therapy (Letter). JAMA 239:2241-2242, May 26, 1978

9. Weber MA: Blood pressure rebound following withdrawal of antihypertensive treatment (Letter). JAMA 239:833, Feb 27, 1978

10. Whitsett TL, Chrisvanthankopoulos S: Evaluation of abrupt cessation of therapy with clonidine. Clin Pharmacol Ther 17: 119, 1979

11. Whitsett TL, Chrysant SG, Dillard BL, et al: Abrupt cessation of clonidine administration: A prospective study. Am J Cardiol 41:1285-1290, Jun 1978

12. Hoobler SW, Kashima T: Central nervous system actions of clonidine in hypertension. Mayo Clin Proc 52:395-398, Jun 1977

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Dr. Steinberg Replies

To the Editor: Dr. Houston's letter raises several important points that need clarification. Semantics are a problem in this field, but our report is not a simple case of hypertensive medication being stopped and restarted. In our patient, the cause of the hypertension, which was excessive renin from end-stage kidneys, was removed. Severe postoperative hypertension in a patient who is volume depleted by dialysis, who has no measurable renin and who still has a blood pressure of 270/120 mm of mercury, should not be confused with the more common rebound and overshoot hypertension that occurs when a patient simply stops taking his antihypertensive medication.

Although we are also familiar with the reports of severe high blood pressure when other drugs are suddenly discontinued, the cited references are not germane to our case. Dr. Houston is talking about rebound or overshoot hypertension and we described a singular circumstance in which severe and unremitting hypertension is related to catecholamines and drug withdrawal rather than a static state of sodium balance or the renin-angiotensin system. It was the uniqueness of this clinical setting of dialysis and bilateral nephrectomy that makes our remarks about clonidine and catecholamines justified. If the postoperative hypertension in this patient was not due to catecholamines or increased sympathetic discharge, what was it due to?

Finally, I doubt that our brief report could have been titled "Propranolol Withdrawal Complicating Bilateral Nephrectomy" as our patient was receiving propranolol after surgical operation and still required nitroprusside and phentolamine for acceptable blood pressure control to be achieved. This control was not accomplished until the seventh postoperative day when clonidine administration was reinstituted.

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Refer to: Nelson AR: Perceptions on PSRO (Informed Opinion). West J Med 131:451-454, Nov 1979

Informed
OPINION

Perceptions on PSRO

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THE PROFESSIONAL STANDARDS REVIEW ORGANIZATION (PSRO) program finds itself in 1979 assailed by a host of challenges, with the more threatening assaults coming from the left more than the right.

Organized *consumerism* won the first round in a demand for PSRO data. Federal Judge Gerhardt A. Gesell, on April 25,1978, ruled in favor of Ralph Nader's Public Citizens' Health Research Group and against the Washington, DC, PSRO (National Capital Foundation) when he determined that PSRO's are government agencies for purposes of the Freedom of Information Act (FOIA). The Health Research Group had demanded publication of such PSRO data as surgical mortality rates and lengths of stay for common diagnoses for identified hospitals and physicians. Judge Gesell indicated that relief from his ruling should be sought by legislative action, if, indeed, PSRO's should be excluded from the FOIA. A second part of his ruling—whether such data identifiable to physician and hospital are exempt under the provisions of the FOIA even though PSRO's are considered as agencies of government—is yet to be handed down. If PSRO data are not exempted in subsequent rulings by Judge Gesell, this may bring an end to any useful quality assessment activity by PSRO's.

Congress, ignoring the explicit responsibility assigned to PSRO's in PL 92-603, is demanding of them a rationing role which they are not, nor have ever been, able to fill simply because rationing was not their intended function. Even those in the bureaucracy responsible for implementing the program (with their ranks substantially depleted by the transfer of the Health Standards and Quality Bureau to Baltimore) seem to be measuring the adequacy of PSRO's on an elusive yardstick of "cost effectiveness." The earlier goal of quality assurance is now only vaguely alluded to as a byproduct of efforts toward cutting utilization of medical services. Leonard D. Shaeffer, director of the Health Care Financing Administration of the Department of Health, Education, and Welfare (DHEW), told the National PSR Council in May 1979 that PSRO's have "basically done a good job" but that his agency is committed to weeding out the nonperforming PSRO's. Citing the costs of the program, he said PSRO's must demonstrate their "impact on overutilization." Also, the 1978 PSRO Program Evaluation states that "The current political climate appears to stress the utilization control mission of the PSRO program in the context of developing a national strategy to reduce the growth of health care expenditures."[1]

Whereas the conservatives within organized medicine formerly comprised a significant challenge to PSRO acceptance by the medical profession (and, thereby, to successful implementation of the program) the unrealistic demands by lib-

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erals within the public at large now constitute the major concern of PSRO proponents. Does this mean that the PSRO program is on its last legs? I do not think so. At least, funding for the program seems assured for the immediate future with an estimated 152 million dollars for fiscal year 1980. Has the scope and direction of program intent changed in the past six years? Undeniably. Will physicians continue to have a role in the review of their professional activity, with their decisions binding upon the payment source? That remains to be seen.

Changing Program Goals

The initial idea for the PSRO program originated in Chicago in 1969 when Senator Wallace F. Bennett accepted the assignment from the Senate Finance Committee of devising a method of dealing with Medicare fraud and abuse. One obvious alternative to direct government inspection was the formation of local organizations of physicians which would conduct peer review and certify that the care received under government sponsored health programs was necessary and appropriate. As the Bennett Amendment was introduced into consecutive sessions of Congress in 1970 and 1972, the assumption gradually emerged that there was substantial overutilization of services by providers. There were absolutely no data available that could show that PSRO's would be able to find and eliminate significant unnecessary expenditures for health care. The idea that *underutilization* would be uncovered by PSRO's, and consequently increase program costs, was considered only half seriously. Thus, the expectations of PSRO held by lawmakers were no longer for a system of accountability and certification of appropriateness, but, rather, for one which would provoke change in the system and save money, even though the potential for savings was only guessed at.

To the surprise of DHEW officials (who opposed passage of the Bennett Amendment and instead preferred a staged implementation with experimentation and evaluation of alternative peer review strategies) the Bennett Amendment was passed in 1972 as part of the Social Security Amendments (PL 92-603). The intervening seven years have seen the establishment of PSRO's in all areas of the country except Nebraska. From an earlier DHEW attitude of laissez-faire, with virtual autonomy of the functioning PSRO's, the trend has been toward rigidity and reliance on a flood of transmittals (policy advisories) to insure uniformity of implementation. Consequently, the opportunities for innovation and an imaginative quasi-research orientation which originally stimulated physician participation were lost, as some PSRO's seemed almost to be formed by *cloning*.

As there has been pressure on PSRO's to comply with standardized procedures, so there is now pressure on them to alter the scope of their peer review activities. The earlier priority was utilization review and quality assurance designed to improve the performance of the *majority* of physicians. In 1973 and 1974, Henry Simmons, then Deputy Assistant Secretary for Health, emphasized that the primary goal of the PSRO program was to improve the quality of medical care at all levels of performance. Cost savings would likely also occur, he reasoned, because unnecessary care would be diminished. Earlier, debate among health services researchers had centered on whether peer review should attempt to identify only the *black hats* (those practicing at the margin of acceptability and worse) or whether peer review data should reflect performance of the majority and serve as the basis for broadly directed education programs. The emphasis now appears to have changed to a hunt for peripheral behavior, focusing on the "outlier" physician who overutilizes services or on those procedures, particularly surgical, where profiles seem to indicate excessive usage.

"If those profile data being collected by the PSRO must also be collected by the fiscal intermediary as part of the payment process, cannot utilization abuse be detected more efficiently in the office of the fiscal intermediary than by a PSRO?" This question, asked frequently in high level DHEW offices over the past year, suggests that the very heart of PSRO review capability—management of the data system, and modification of that system on a continuing basis—is vulnerable. The logical next question—how the profile data should be acted upon—does not seem to intrude into the discussion. If PSRO's lose certification capability, are we not then back, full circle, to a consideration of a system of retrospective denial similar to that which made shotgun-blast errors in the early 1970's? Is not the tentative effort by government to require Uniform Hospital Discharge Data Set (UHDDS) information on all private patients even more significant in this context?

If the earlier intent to decrease unnecessary

care and assure that the quality of such care met professionally accepted standards has given way to a regimented system which seeks to focus efforts on limiting expensive services, the locus of primary operational authority for professional standards review has also changed.

The Hospital as the Functional Unit

The intent of the PSRO legislation held that local groups of physicians would implement peer review in hospitals in their area. Early meetings of the National PSR Council were inevitably attended by representatives of the American Hospital Association (AHA). They appeared to view debate over each developing interpretive policy only in terms of its application toward the ultimate position of hospitals as the dominant force in the implementation of PSRO. This sometimes led to a curious inconsistency in the position taken by AHA representatives on consecutive topics, according to my recollections. At any rate, the physician group (that is, the PSRO) was to be the implementing body, not the hospital. With the delegated hospital emerging as the basic functional unit in most PSRO's, however, the PSRO itself has been often relegated to a role of data analysis and overseer. This often results in an adversary position with the hospitals themselves. Rather than acting as a prime mover at the community level, assisting in the conduct of area-wide quality assurance activity, the PSRO has become another *Inspector General*. In only a few areas have PSRO's been funded to conduct directly utilization review and quality assessment, selecting review coordinators and physician advisors cooperatively with the hospital rather than being relegated to a *check off* role.

The overlapping roles of PSRO, the Joint Commission on the Accreditation of Hospitals (JCAH) and state accrediting bodies have led to push-and-shove among the *inspectors,* leaving physicians and hospitals confused and angry. Although representatives of JCAH and DHEW met frequently over the years, making repeated efforts to coordinate their individual demands for medical care evaluation, JCAH appeared to have the most secure position in the dialogues. In the field, JCAH inspectors often simply ignored PSRO's as being unimportant or as having different objectives. Both PSRO and JCAH made the mistake of playing a *numbers game,* requiring a certain number of studies regardless of their worth. This policy has only recently been altered by JCAH, in a new Quality Assurance Standard adopted in April 1979. The new standard emphasizes an approach which must "focus on the resolution of known or suspected problems" rather than use of a particular format.

Nonphysician Supporters of PSRO Are Few

The schizoid attitude of organized medicine has gradually given way to a position of support. The American Medical Association's House of Delegates, in December 1978, approved a report recommending "strong support for continuation of the PSRO program as a professionally directed effort to assure the quality and appropriateness of care provided to patients." There was no dissent, although reference committee testimony still reflected the thinking of a few diehard, anti-PSRO members.

Still, there is often failure to recognize that physician management of the peer review process is exceedingly vulnerable and has few supporters outside the physician community. This foothold for the medical profession is unique. Consider the areas of health care system subject to government regulation and the role of physicians in each:

- Facility authorization rests solidly with the State Health Planning and Development Agency. The role of physicians in Health Service Agencies (HSA's) is token compared with the enormous influence wielded by local elected officials and hospital special interest groups.

- Manpower regulation, whether at the undergraduate or graduate level, is controlled by DHEW and the congressional appropriations committees. Volume, specialty mix and ultimately physician placement in underserved areas (via National Health Service Corps or, in the near future, through the state licensure process) are totally outside the influence of organized medicine.

- Fees. The Federal Trade Commission has lifted even relative value analysis from the hands of physicians. Negotiated fee schedules, which are such an important part of Kennedy's and Carter's proposals for national health insurance, will in a few years leave job action as the only recourse to accepting the terms of government.

Only in the determination, on a case by case basis, of the appropriateness of services delivered to patients do physicians have a binding authority. This was not the case before PSRO, when fiscal

intermediaries made retrospective judgments with very little challenge.

What Is the Future?

If PSRO is the sole area in which regulation of health care is substantially influenced by practicing physicians, what is the future of the PSRO program likely to be? Central direction of the program will come under stronger influence of former Social Security Administration personnel (as distinguished from those bureaucrats who formerly were aligned philosophically with the Assistant Secretary for Health). The transfer of DHEW's Health Standards and Quality Bureau (HSQB) to Baltimore, and vacancies created by that transfer, make this a reasonable guess. Administration of the PSRO program by the HSQB took double barrel blows in 1977 and 1978 when allegations of the ineffective and tardy implementation of the program were followed up by orders to move HSQB to Baltimore. Positions vacated as a result of poor morale were added to by resignations from those unwilling to move. This resulted in severe personnel shortages at all levels, but particularly in the areas where familiarity with quality assurance methods and health services research was needed.

The National PSR Council will function largely as a "reactor panel" and will have a weaker voice in setting policy direction.

Individual PSRO's will be under increasing pressure to provide cost-effectiveness justification. More PSRO's will be faced with termination proceedings. (As of July 1979, termination proceedings were underway for Tennesee Foundation for Medical Care, Erie Region PSRO (Buffalo), Calumet Area PSRO (Indiana) and Area 19 (Long Beach) California PSRO. Mismanagement will be the alleged basis for many of these determinations, and physicians on boards of directors will be accused of not adequately monitoring the activities of PSRO staffs.

Where a PSRO is to be replaced by an alternate organization, the nature of that alternate is yet to be clarified. The Medicaid agency and the fiscal intermediary are obvious possibilities.

Balancing this pessimistic view, however, is the fact that some PSRO's are well managed, have substantial physician support and, most important, are viewed by community leaders as representing a positive and important effort by the medical profession to provide peer review. The skepticism held by hospital administrations and private insurers appears to be increasingly balanced by a knowledge of alternatives far worse than PSRO.

Organized medicine appears to be taking a more supportive posture.

Congress, while it voices ultimatums regarding the need for demonstrated cost effectiveness, may yet recognize that the alternative to hospital-based utilization review is retrospective denial or counterproductive sanctions. And many are aware of the grief inherent in this alternative.

The large threat to PSRO, as I see it, is the pressure from DHEW to identify perceived over-utilization and apply punitive measures. This will erode the fragile base of physician support, and broadly supported educational approaches may give way to a "those guys versus us guys" mentality, with PSRO's on one side and delegated hospital staffs on the other.

If this were to become the prevailing situation, passive resistance by hospital staffs, coupled with fears of the loss of confidentiality of sensitive data, would bring meaningful quality assessment activity by PSRO's to a halft. Gradually, utilization review authority would be vested in a small cadre of consultants. Because the profiles upon which utilization review judgments are based can be as easily collected by the fiscal intermediary, this last portion of our management responsibility would also be lost to us, as the fiscal intermediary assumed the decisive role. Then PSRO's, relics of an idealistic concept, would exist only as organizational diagrams with no authority and no physician support.

REFERENCE

1. Professional Standards Review Organization 1978 Program Evaluation, DHEW Pub No HCFA-03000. US Dept of Health, Education, and Welfare, Health Care Financing Administration, Jan 1979, p 2

Refer to: Potts M: Changing attitudes toward abortion (Controversial Issues in Medicine). West J Med 131:455-459, Nov 1979

Changing Attitudes Toward Abortion

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INDIVIDUAL AND SOCIAL ATTITUDES toward abortion are unstable. Perhaps it is the difference between individual and social perspectives, combined with the special ethical problems posed by balancing the welfare of an adult against the potential of the embryo and fetus, that contributes to this instability. The purpose of this paper is to document key changes in medical attitudes regarding abortion and then to seek the foundations of a consistent social policy towards its availaability.

Abortion has had a long history, is one of the most common surgical procedures done and is likely to remain with us for a long time. It is indisputable that induced abortion has played an important role in the decline of fertility in Western countries, even during the many years that the operation was illegal.[1,2] There is strong evidence that abortion (whether licit or illicit) is now making a substantial contribution to fertility changes in contemporary developing countries. For example, in a recent study of village abortionists in Thailand it was estimated that there are at least 1,000 traditional abortionists in that country and that they may be carrying out more than 250,000 abortions a year (32 abortions per 1,000 women aged 15 to 44, or 214 abortions per 1,000 live births).[3] Of course, in the cities the rates would be even higher.

EDITOR'S NOTE: *Based on a presentation at the 1979 Annual Meeting of the California Medical Association, this paper presents a longitudinal overview of this controversial topic.*

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Past Attitudes

While the abortion procedure itself has been a long-standing and increasingly important aspect of human family and communal history, medical attitudes have varied widely. The story behind these changes is greatly different from the superficial assumptions of most commentators.

Abortion appears to have been accepted in a matter-of-fact, though little spoken of, manner by North Americans and Europeans in the early 19th century. In Britain, abortion before quickening (the first recognizable movement of the fetus, usually appearing from the 16th to the 18th week of pregnancy) was not a felony. A series of parliamentary acts (1803, 1828 and 1837) led up to the antiabortion legislation of 1861 which remained in force for nearly 100 years.[4] The early legislation appears to have raised little interest beyond a tiny circle of parliamentary draftsmen. The 1803 act mixed legislation on abortion, arson and poisoning, and the act of 1828 dropped the previous distinction between before and after quickening. It is notable that there were no lay, religious or medical comments on the restrictive legislation of 1861 which was to remain in force, nor was it discussed on the floor in Parliament. Abortion was not a major public issue; it did not present insuperable theological problems, and at least some of the British medical profession continued to believe that therapeutic abortion was a licit operation. "When it [abortion] is the only method of saving the life of the mother," stated a commonly used medical textbook in 1911, "or when without it her life is

placed in imminent danger, it is usually regarded not only as justifiable but as imperative."

Mohr[5] has documented the revolution in medical attitudes that took place during the 19th century in the United States. In 1800 abortion was legal and available in every state of the Union. Initially, legislation dealing with abortion did not attempt to outlaw the procedure or to limit abortion per se, but rather to deal with cases where, for example, an abortifacient medicine might prove poisonous to the mother or where a surgical attempt at abortion might prove lethal. The 1828 legislation in New York began as a draft statute against "every person who shall perform any surgical operation by which human life shall be endangered, such as the amputation of a limb or of the breast," but was modified in debate, presumably by the medical lobby, so that in the final statute only abortion was mentioned, perhaps because it was still a rare operation. Specifically, the law included the phrase "unless the same [the abortion] shall have been necessary to preserve the life of such women."

There is qualitative evidence that as the century progressed, abortion rates rose and abortionists began to advertise widely. Any woman seeking an abortion had to look no further than the pages of her local city press. It was the emerging qualified practitioners who began using state laws to restrict the activities of the numerous abortionists. The tragedies that undoubtedly occurred gave rise to some of the first examples of sensational journalism.

The American Medical Association (founded in 1847) attracted a young physician named Horatio Robinson Storer, who began to crusade within the AMA for restrictive abortion legislation. He did not receive unanimous support. His opposition within the AMA complained that he and his followers seemed "to have thrown out consideration of the life of the mother, making that of the unborn child appear of far more consequence, even should the mother have a dozen dependent on her for their daily bread." But, as is often the case, the enthusiasts won out over the silent majority, who wrongly assumed that the antiabortionists "would fail to convince the public that abortion in the early months of pregnancy is a crime."

The antiabortion movement was politically right of center. Abortion, like all forms of fertility regulation, began among the affluent, and the antiabortionists feared small families among the rich would lead "the ignorant, the low-lived and the alien" to take over America, so that "the Puritanic blood of '76 will be but sparingly represented in the population." Storer's general attitude toward women is reflected in his fight against their entry into medicine.

A largely impassive public looked on, and religious leaders were in no hurry to join the trumpeting armies of physicians assembling behind Storer under the AMA banner. Only slowly did attitudes change. By the 1870's the Catholic church was beginning publicly to condemn abortion and to categorize it as murder; but even into the 1880's the Protestant leadership remained, on the whole, outside the debate. Antiobscenity groups were more vigorous allies of antiabortion legislation, particularly such men as Anthony Comstock, whose laws against contraception were to remain anachronisms for a century.

By 1900 abortion had become illegal in every state of the Union. In a sentence, antiabortion legislation in the United States was an expression of restrictive trade practices within the medical profession—jealous of the profits made by abortionists and encouraged by a burgeoning daily press hungry for sensational stories—while most church leaders watched from the sidelines.

In historical terms, abortion was outlawed at the very moment when it became most urgently and universally needed. Of the women marrying in Britain in 1860, a quarter were destined to bear eight or more children. Among their great-granddaughters marrying in 1925, more than two thirds were to have one, two or no children at all. The birthrate in England and Wales fell from 28.7 in 1900 to only 14.4 per 1,000 in 1933—a decline of 50 percent. In the United States the birthrate fell to between 18 and 19 per 1,000 in the 1930's. With contraceptives less available and less effective than today and sterilization rarely available, there can be no doubt that abortion was common and demographically significant.

In 1898 the Chrimes brothers, who sold "Female tabules . . . positively unequalled for all FEMALE AILMENTS, the most OBSTINATE obstructions, irregularities, etc. of the female system," attempted to blackmail more than 8,100 British women for buying their remedy. The police intercepted hundreds of pounds paid by frightened women who had had abortions. One victim, typical of hundreds, wrote "I promise not to repeat

what I have done as long as I live. . . . I should not like my missus [employer] to know, else I shall lose my situation." In 1914 a single chemist in one town (Burnley) in one year admitted selling 500 doses of diachylon—a lead-based abortifacient associated with an epidemic of poisoning in Britain before the First World War. The evidence from the United States for frequent abortion is equally persuasive.

Abortion was not, as seems to be a contemporary perception in some quarters, an invention of the US Supreme Court in 1974; nor would it be likely to disappear if legal services were curtailed, laws restricted or constitutions amended.

Contemporary Changes

By the time abortion was made legal in Britain in 1967, and the New York law was repealed in 1970, the demand for abortion, at least among the married, was probably less than it had been a generation earlier.

On the whole, attitudes in the United States evolved from a more conservative starting point than in Britain, but have since changed more rapidly. In Britain therapeutic abortion—especially after 1938 when it was supported by the precedent of the Bourne judgment—became more common than in the United States before the reform and repeal legislation of the late 1960's. It was for this reason, perhaps, that Britain adopted vacuum aspiration more slowly than the United States; many British physicians had done a considerable number of dilatation and curettage (D and C) operations before the 1967 reform.

The attitudes of British and American physicians in the 1960's and 1970's have been documented in a number of surveys.[1] In Britain, doctors were not in the forefront of abortion reform. Most obstetricians and gynecologists opposed the introduction of the 1967 law and many general practitioners were unenthusiastic. Yet a decade later, most members of the Royal College of Obstetricians and Gynaecologists supported the existing legislation when attempts were made to reverse it. Family practitioners have given particularly strong support to abortion legislation, probably because they see the social need for the procedure more vividly than anyone else. The British Medical Association, which was not a friend of reform in 1967, resolved in 1978 "that legislation is not desirable at the present time to amend [restrict] the Act."

In the United States physicians played a larger role in reform and repeal movements at the state level before the US Supreme Court judgment in 1973. The Planned Parenthood Federation of America, for example, supported abortion reform while the Family Planning Association in Britain buried its head in contraceptives, if not in sand. As in Britain, the experience of clinical practice in situations where abortion is legal has reinforced support of liberal legislation.

On the whole, the public, like the medical profession, has either become more liberal in its views towards abortion or has remained relatively consistent in its moderate attitude with small minorities voicing strong opinions either for or against abortion. Most people have a pragmatic attitude, combining the wish that the problem would go away with a preference for legal over illegal operations.

Will History Repeat Itself?

In the United States, and to some extent in the rest of the English speaking world, the mid-19th century campaign that Storer mounted to introduce restricted abortion legislation is being repeated. There is a chance that public attitudes will be influenced for a second time by a vocal few, who seek unrealistically simple solutions to the complex problem of abortion by means of a few slogans linked with a sensation-seeking press. Today, abortion is better understood and much safer than it was in the last century, which should make such a campaign more difficult to mount. Yet, paradoxically, the contemporary Right to Life movement has a much more vigorous support from some arms of the church than it enjoyed a hundred years ago.

The current, passionate public debate on abortion in the United States and, to a lesser extent, in other Western countries, is an aberration of the affluent. It has no analogue in the developing world. It is only when a considerable middle class emerges—as is happening in Colombia, South America, for example—that the brutal realities of poverty and the problems of fertility regulation can be forgotten by the fortunate, or by the smug, some of whom espouse such seductive slogans as "abortion is murder." According to a personal communication from J. Flavier, Associate Director for Rural Reconstruction, and former president of the Family Planning Organization, Republic of the Philippines, a recent sur-

vey of *barrio* women in the Philippines showed that more than half of them thought that abortion was legal in their country, so common and accessible is the procedure (although done painfully and dangerously).[6] The Philippines, of course, retains the antiabortion legislation which it received as an American possession.

What Can the Medical Profession Do?

In the past, the minority of the medical profession who strongly opposed abortion often aroused the pragmatic majority to action because of the visibility that high monetary profits give abortionists. Comstock's pursuit in the 19th century of the New York abortionist Madam Restell exemplified such a situation; part of the backlash in Britain against the 1967 Reform Act reflects the same attitudes.

Aspects of abortion as a surgical procedure reinforce the commercial instincts of some physicians: abortion is a replicable, predictable operation done on healthy patients who have made their own diagnoses. A well-organized abortionist and assistant providing a needed service can do 10 to 20 first-trimester operations in a day. If their fee is directly related to that charged for other comparable surgical procedures, they will reap generous rewards—and overcharge. Most other operations treat disease and, because each patient is different, a variety of skills is needed for determining a correct diagnosis and treatment. In the United States today, legal abortions are too expensive. The operation is not worth $250, or even $100—certainly not in clinics where ten or more are being done each day. For a while, profits may appear attractive, but in the long term the temptation to take easy money will boomerang on providers of this service. Simple human envy of persons earning a lot of money makes it relatively easy for the opposition minority to slowly recruit growing numbers of the pragmatic majority to their cause.

But perhaps the most important role of physicians, a privileged group with an unusually prolonged education, special insights into the gamut of human problems and a specialized knowledge of embryology, is to help establish a liberal and civilized framework within which colleagues of different persuasions can make free and objective choices regarding the delivery of abortion services. Ethical considerations should continue to evolve with thorough discussion of the advisability of offering or refusing abortions to their patients. Physicians must participate in political and administrative decisions that are broad and well founded, rather than the result of narrow, single-choice presentations of complex issues.

Societal and Individual Responsibility

No one is "proabortion" any more than "procancer." In such an emotive issue it is easy for ingenuous and passionate people to sully the precision of the English language. Dr. Carolyn Gerster, President of Right to Life, said at a 1979 meeting of the California Medical Association that "Abortion *on demand to term* is not the will of the American people" (emphasis added). Ultimately, tiny but illegitimate additions to an argument become the virus that infects the majesty of the law, threatens to erode the balance of politics and might even set back 400 years of hard-won religious toleration.

In the abortion dispute the basic facts of embryology are not in dispute, but strong and sincere differences about whether abortion should be available do exist. Protagonists rarely change sides. "It is a woman's *right* to have an abortion," say many feminists. "Abortion is murder," say those who assert a *right* to life. At first glance, each assertion gives the mother, or her child, total rights over the other party and preempts all further discussion. What should society do when an irresistible minority meets an immovable minority?

It is not a new problem. All the great religions make somewhat different assertions about the world in which we live. The way to heaven is *not* the same for a Muslim and a Christian, and each differs from the beliefs of a Buddhist or a Hindu. Abortion should be an issue to be discussed in committees, preached about from the pulpit, written about in academic journals or read about in the daily paper, but never a topic to incite arson or physical violence—any more than differing religious beliefs should be justification of persecuting those holding them. Wars of religion should be anachronistic.

In 1971, the US Supreme Court overturned all antiabortion state laws as unconstitutional. The Court did not say abortion was right or wrong. It dealt, instead, with the creation of an environment in which society could make its own choices. The Court wrote "We need not resolve the difficult question when life begins. When those trained

in the respective disciplines of medicine, philosophy and theology are unable to arrive at any consensus, the judiciary, at this point in the development of man's knowledge, is not in a position to speculate to the answer."

The Catholic thinker, Daniel Callahan, made the same point when he wrote "To say, for instance, that God forbids the taking of 'innocent' life, while conceding—as I think we must—that it is left up to man to define what an 'innocent' life is, is to fail to see that the only possible *meaning* this rule could have is the meaning human beings *choose* to give it."[6]

Physicians, like theologians, interpret their knowledge of embryology to suit their previous beliefs. "Fertilization is the key moment in development," say antiabortion thinkers, "beyond which the embryo must be accorded the rights of a person." "Fertilization can give rise to placental tissue, without an embryo and a teratoma may be genetically unique," reply the prochoice believers.[7]

In the last analysis the abortion debate revolves around unprovable interpretations of observable facts; it is an exercise in religious toleration, and it should be no more surprising to find an abortion clinic in a city where a substantial number of people are sincerely opposed to the operation, than it is to find a church, a mosque and a synagogue on the same street. We must respect the opinions of others while preserving the liberty of individual persons to decide on complex, subtle and difficult topics. Slogans can only degrade our decision making. Threats to rouse the voting public against a "hit list" of politicians because of their voting record for, or against, the single issue of abortion jeopardize the long, and largely successful, evolution of party politics. "I believe in America," President Kennedy said, "where no Catholic prelate . . . and no Protestant minister would tell . . . parishioners for whom to vote."

Responsibility arises only when individual persons make choices. The record of history shows that couples make better decisions than the State about most aspects of reproduction. No one wants policemen in every bedroom. There is no need to be afraid of the new choices that result from an increased understanding of biology; our expanding knowledge of reproduction can only contribute to the health and welfare of each person and of society.

REFERENCES

1. Potts M, Diggory P, Peel J: Abortion. New York City, Cambridge University Press, 1978

2. Van der Tak J: Abortion, Fertility, and Changing Legislation. Lexington, Lexington Books, 1974

3. Tongplaew Narkavonnakit: Rural Abortion in Thailand: National Survey of Practitioners (1979). Research and Evaluation Unit, National Family Planning Program, Bankok, 1979

4. William G: The Sanctity of Life and the Criminal Law. London, Faber & Faber, 1958

5. Mohr J: Abortion in America. New York City, Oxford University Press, 1978

6. Callahan D: Abortion: Law, Choice and Morality. New York City, Macmillan, 1970

7. O'Mahony PJ, Potts M: Abortion and the soul. Month 38: 45, 1967

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in memoriam

Brown, Louise P., Santa Barbara. Died January 29, 1979 of arteriosclerosis, aged 88. Graduate of New York Medical College and Hospital for Women, New York, 1913. Licensed in California in 1943. Dr. Brown was a member of the Medical Society of Santa Barbara County.

Dewey, Edward B., Pebble Beach. Died March 1, 1979 of bronchopneumonia, aged 83. Graduate of the University of Colorado School of Medicine, Denver, 1919. Licensed in California in 1928. Dr. Dewey was a retired member of the Los Angeles County Medical Association.

Doyle, Gerald Francis, Sacramento. Died September 14, 1979 in Sacramento, aged 71. Graduate of Loyola University School of Medicine, Chicago, 1936. Licensed in California in 1936. Dr. Doyle was a retired member of the Sacramento County Medical Society.

Fanson, Anne Ethel, Pasadena. Died January 9, 1979 of cerebral thrombosis, aged 88. Graduate of Rush Medical College, Chicago, 1923. Licensed in California in 1924. Dr. Fanson was a member of the Los Angeles County Medical Association.

Frick, Donald J., jr., Los Angeles. Died September 18, 1978 of fibrosarcoma, aged 67. Graduate of Harvard Medical School, Boston, 1941. Licensed in California in 1941. Dr. Frick was a member of the Los Angeles County Medical Association.

Friedberger, William, Stockton. Died July 24, 1978 of kidney failure, aged 92. Graduate of Cooper Medical College, San Francisco, 1908. Licensed in California in 1908. Dr. Friedberger was a retired member of the San Joaquin County Medical Society.

Hammerly, Fred, North Hollywood. Died August 12, 1979 in North Hollywood, aged 76. Graduate of the University of Wisconsin Medical School, Madison, 1933. Licensed in California in 1940. Dr. Hammerly was a retired member of the Los Angeles County Medical Association.

Hanson, Raulf A., Carmichael. Died February 9, 1979, aged 59. Graduate of the University of Wisconsin Medical School, Madison, 1950. Licensed in California in 1954. Dr. Hanson was a member of the Sacramento County Medical Society.

Henney, James E., San Carlos. Died February 10, 1979 of carcinoma of the epiglottis, aged 58. Graduate of the University of Virginia School of Medicine, Charlottesville, 1949. Licensed in California in 1953. Dr. Henney was a member of the San Mateo County Medical Society.

Hesselberg, Erwin H., San Francisco. Died July 8, 1978, aged 42. Graduate of the University of California, San Francisco, School of Medicine, 1966. Licensed in California in 1967. Dr. Hesselberg was a member of the San Francisco Medical Society.

Ingle, Wilfred G., Corning. Died March 16, 1979 of circulatory failure, aged 60. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1945. Licensed in California in 1945. Dr. Ingle was a member of the Tehama County Medical Society.

Jordan, John H., Lewiston. Died July 19, 1979 in Sacramento, aged 62. Graduate of the Creighton University School of Medicine, Omaha, 1943. Licensed in California in 1944. Dr. Jordan was a retired member of the Shasta-Trinity County Medical Society.

Koerper, Victor Eugene, Oakland. Died July 29, 1979 in Sonoma, aged 65. Graduate of the University of Rochester School of Medicine and Dentistry, 1940. Licensed in California in 1941. Dr. Koerper was a retired member of the Alameda-Contra Costa Medical Association.

Nugent, Maurice W., Los Angeles. Died August 26, 1979 in Los Angeles, aged 70. Graduate of the University of Toronto Faculty of Medicine, 1934. Licensed in California in 1944. Dr. Nugent was a member of the Los Angeles County Medical Association.

Paul, Carl J., Orange. Died September 4, 1979, aged 70. Graduate of the University of Southern California School of Medicine, Los Angeles, 1935. Licensed in California in 1936. Dr. Paul was a retired member of the Orange County Medical Association.

Rudens, Maurice C., Montebello. Died February 24, 1979 of lymphocytic leukemia, aged 65. Graduate of Rush Medical College, Chicago, 1937. Licensed in California in 1946. Dr. Rudens was a member of the Los Angeles County Medical Association.

Taylor, Alexander, San Francisco. Died September 18, 1979 in San Francisco of cancer, aged 52. Graduate of the University of Edinburgh Faculty of Medicine, Edinburgh, 1949. Licensed in California in 1957. Dr. Taylor was a member of the San Francisco Medical Society.

Thorne, George W., Duarte. Died April 6, 1979 of aspiration pneumonia, aged 86. Graduate of the University of California Medical School, Berkeley-San Francisco, 1925. Licensed in California in 1925. Dr. Thorne was a retired member of the Alameda-Contra Costa Medical Association.

Walker, Samuel J., Whittier. Died March 31, 1979 of myocardial infarction, aged 82. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1928. Licensed in California in 1928. Dr. Walker was a member of the Los Angeles County Medical Association.

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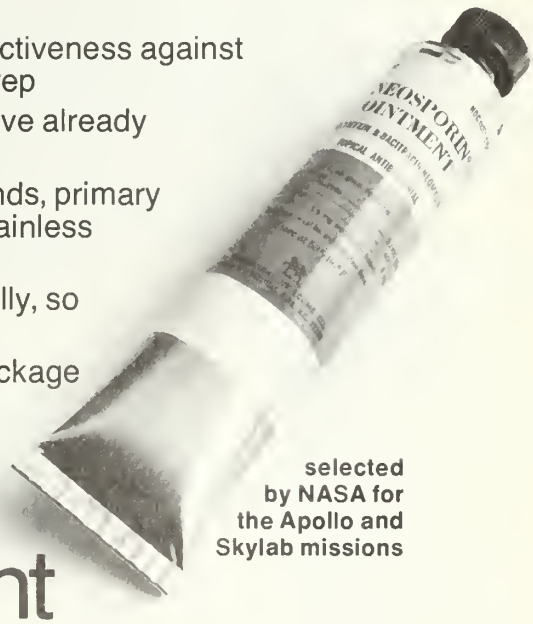

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When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

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Brief Summary of Prescribing Information

DESCRIPTION Each tablet of PERCOCET®-5 contains 5 mg oxycodone hydrochloride (WARNING: May be habit forming), 325 mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS. 6085 BS

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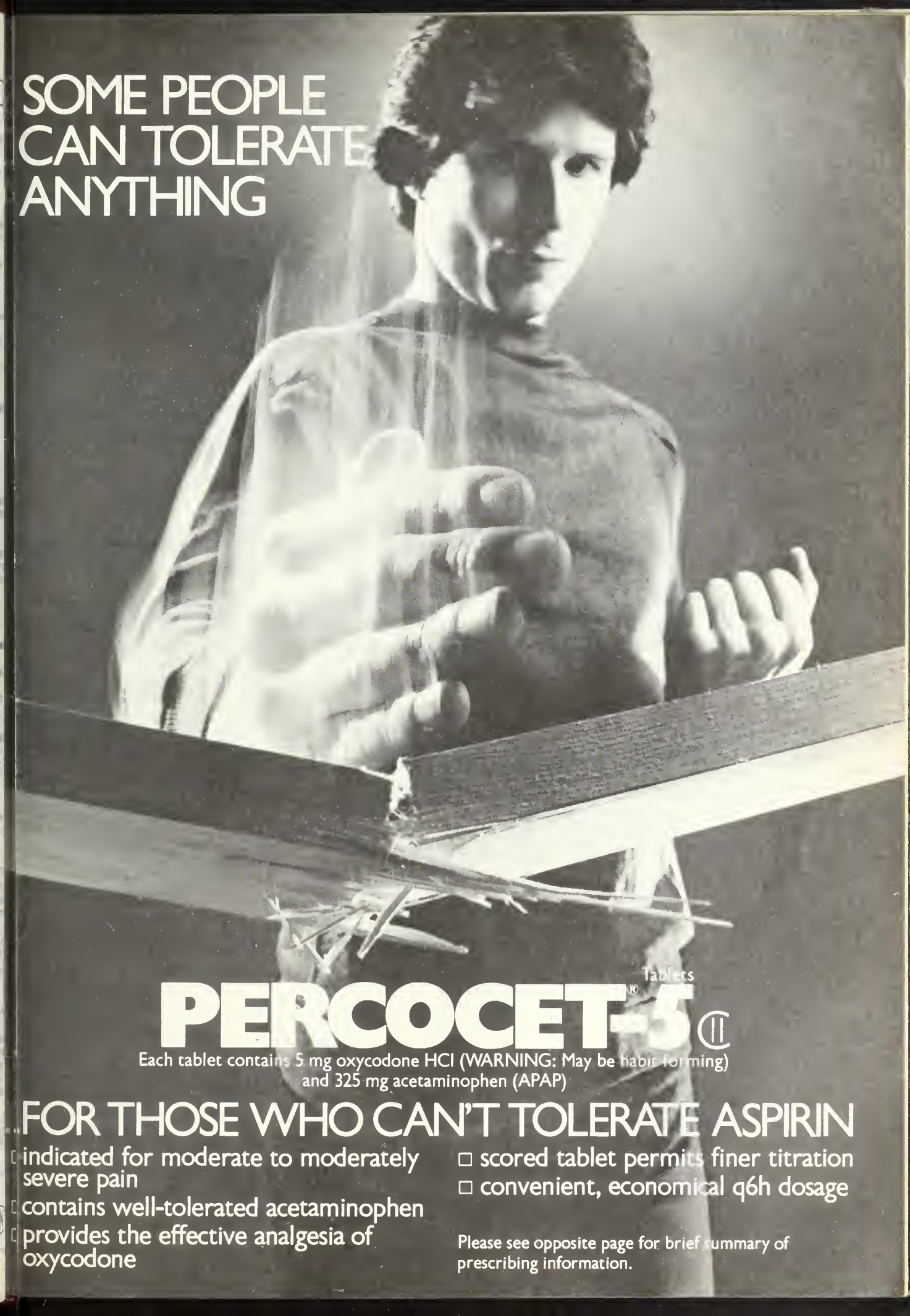
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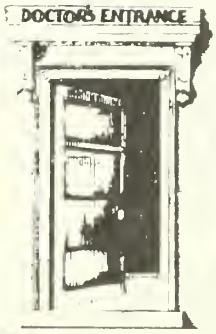

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANTIMICROBIAL PRESCRIBING—Harold C. Neu, MD, Professor of Medicine and Pharmacology, Columbia University; Head, Division of Infectious Diseases, Columbia-Presbyterian Medical Center, New York. Antimicrobial Prescribing, Inc., P.O. Box 3153, Princeton, NJ (08540), 1979. 111 pages, $19.95.

BIRTH OF A FAMILY: THE NEW ROLE OF THE FATHER IN CHILDBIRTH—Nathan Cabot Hale. Anchor Books, Doubleday & Co., Inc., 245 Park Avenue, New York City (10017), 1979. 195 pages, $7.95 (paperback).

CLINICAL CARDIOLOGY—Second Edition—Maurice Sokolow, MD, Professor of Medicine Emeritus, Senior staff member, Cardiovascular Research Institute; Formerly Chief of Cardiology and Program Director of the USPHS Clinical Cardiology Training Program, University of California, San Francisco; and Malcolm B. McIlroy, MD, Professor of Medicine, Senior staff member, Cardiovascular Research Institute, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1979. 718 pages, $17.50.

CURRENT NEUROLOGY—Volume 2—Edited by H. Richard Tyler, MD, Professor of Neurology, Harvard Medical School; Head, Section of Neurology, Peter Bent Brigham Hospital, Boston; and David M. Dawson, MD, Associate Professor of Neurology, Harvard Medical School; Physician, Section of Neurology, Peter Bent Brigham Hospital. Houghton Mifflin Professional Publishers, Medical Division, Two Park St., Boston (02107), 1979. 531 pages, $34.00 (US), $42.50 (elsewhere).

DR. FISHBEIN'S POPULAR ILLUSTRATED MEDICAL ENCYCLOPEDIA—Morris Fishbein, MD. Doubleday & Co., Inc., 245 Park Ave., New York City, (10017), 1979. 773 pages, $14.95.

GENETIC COUNSELING: FACTS, VALUES, AND NORMS in Birth Defects: Original Article Series—Editors: Alexander M. Capron, LLB; Marc Lappe, PhD; Robert F. Murray, Jr., MD, MS; Tabitha M. Powledge, MS; Sumner B. Twiss, PhD, and Daniel Bergsma, MD. Alan R. Liss, Inc., 150 Fifth Ave., New York, NY (10011), 1979. 346 pages, $34.00.

BETH ISRAEL CONFERENCE PROGRAM
1980 WINTER SCHEDULE

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FIRST ANNUAL VAIL PATHOLOGY CONFERENCE
February 16-23, 1980, Kiandra-Talisman Lodge, Vail, Colorado
TENTH ANNUAL ASPEN RADIOLOGY CONFERENCE
Feb. 23-March 1, 1980, Aspen Institute for Humanistic Studies, Aspen, Colorado
FIFTH ANNUAL VAIL FAMILY PRACTICE CONFERENCE
February 23-March 1, 1980, The Mark, Vail, Colorado
THIRD ANNUAL BETH ISRAEL VAIL CANCER CONFERENCE
March 1-8, 1980, Kiandra-Talisman Lodge, Vail, Colorado
SECOND ANNUAL VAIL SPORTS MEDICINE CONFERENCE
March 1-8, 1980, Lion Square Lodge, Vail, Colorado
FIFTH ANNUAL VAIL GENERAL SURGERY CONFERENCE
March 8-15, 1980, The Mark, Vail, Colorado
SECOND ANNUAL VAIL GERIATRIC MEDICAL CONFERENCE
March 8-15, 1980, Kiandra-Talisman Lodge, Vail, Colorado
FIRST ANNUAL VAIL GENERAL DENTISTRY CONFERENCE
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HANDBOOK OF NONPRESCRIPTION DRUGS—Sixth Edition—American Pharmaceutical Association, 2215 Constitution Ave., N.W., Washington, (20037), 1979. 512 pages, $20.00

THE HIDDEN MINORITY—A Profile of Handicapped Americans—Sonny Kleinfield, The New York Times. Little, Brown and Company, Publishers, 747 Third Ave., New York (10017), 1979. 214 pages, $8.95.

HOW TO IMPROVE YOUR CHILD'S BEHAVIOR THROUGH DIET—Laura J. Stevens and Rosemary B. Stoner. Doubleday & Company, Inc., 245 Park Avenue, New York (10017), 1979. 346 pages, $9.95.

INNER BALANCE: THE POWER OF HOLISTIC HEALING—Editor: Elliott M. Goldwag. SPECTRUM, Prentice-Hall Inc., Englewood Cliffs, NJ (07632), 1979. 360 pages, $5.95 (paperback).

MAN IN FLIGHT: BIOMEDICAL ACHIEVEMENTS IN AEROSPACE—Eloise Engle and Arnold Lott. Leeward Enterprises, Ltd., P.O. Box 149, Annapolis, MD (21404), 1979. 396 pages, $16.95.

MEDICINE BEFORE COLUMBUS—The Weisman Collection of Pre-Columbian Medical Sculpture—Abner I. Weisman, MD. Pre-Cortesian Publications, Inc., 162 E. 95th Street, New York City (10028), 1979. 150 pages, $14.50.

NEW ADVANCES IN THE TREATMENT OF CANDIDAL VAGINITIS—Number 7—Royal Society of Medicine International Congress and Symposium Series: Edited by D. Gough. Published jointly by The Royal Society of Medicine, Academic Press and Grune & Stratton. Grune & Stratton, Inc., Medical and Scientific Publishers, 111 Fifth Ave., New York City (10003), 1979. 38 pages, $9.50.

ONCE A MONTH—Katharina Dalton, MD. Hunter House Inc, Publishers, 748 E. Bonita Ave., Suite 105, Pomona, CA (91767), 1979. 206 pages, $4.95 (paperback).

PARDON MY SNEEZE—The Story of Asthma and Other Allergies—4th Ed.—Milton Millman, MD, allergist practicing in San Diego. Vantage Press, Inc., 516 West 34th St., New York City (10001), 1979. 290 pages, $12.95.

THE PHYSICIAN AND THE MENTAL HEALTH OF THE CHILD—I. ASSESSING DEVELOPMENT AND TREATING DISORDERS WITHIN A FAMILY CONTEXT—Editors: Herbert J. Grossman, MD, James E. Simmons, MD, Allen R. Dyer, MD, and Henry H. Work, MD. American Medical Association, P.O. Box 821, Monroe, WI (53566), 1979. 111 pages, $4.00 (paperback).

RECENT ADVANCES IN THE DEVELOPMENTAL BIOLOGY OF CENTRAL NERVOUS SYSTEM MALFORMATIONS, In Birth Defects: Original Article Series—Editors: Ntinos C. Myrianthopoulos, PhD, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, MD; Daniel Bergsma, MD, Series Editor, The National Foundation-March of Dimes, Birth Defects: Original Article Series, New York City; and Associate Editors. Alan R. Liss, Inc., 150 Fifth Ave., New York City (10011), 1979. 134 pages, $16.00.

REVIEW OF PHYSIOLOGICAL CHEMISTRY—Seventeenth Edition—Harold A. Harper, PhD, Professor of Biochemistry, University of California, School of Medicine, San Francisco; Victor W. Rodwell, PhD, Professor of Biochemistry, Purdue University, Lafayette, Indiana; Peter A. Mayes, PhD, DSc, Reader in Biochemistry, Royal Veterinary College, University of London; and Associate Authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1979. 702 pages, $14.50.

SKIN DEEP—The Making of a Plastic Surgeon—Donald T. Moynihan, MD, and Shirley Hartman. Little, Brown and Company, Publishers, 747 Third Ave., New York (10017), 1979. 339 pages, $10.00.

STOP FORGETTING—Dr. Bruno Furst—Revised and Expanded by Lotte Furst and Gerrit Storm. Doubleday & Company, Inc., 245 Park Avenue, New York (10017), 1972. 340 pages, $5.95 (paperback).

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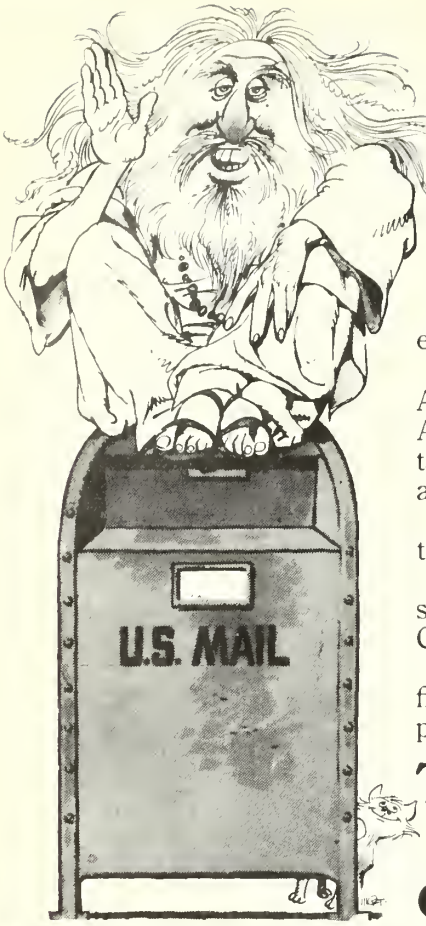

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ANESTHESIOLOGY

January 8-12—**Anesthesia Update.** UCSD at Hotel del Coronado. Tuesday-Saturday. 20 hrs. $200.

January 25-27—**Pediatric Anesthesiology—18th Clinical Conference.** Childrens Hospital at Marriott, Los Angeles. Friday-Sunday. 15 hrs. $160. Contact: Wayne Herbert, MD, P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

February 7-10—**7th Neonatal and Infant Respiratory Symposium.** Ohio State Univ., Dept. of Anesthesiology, at Marriott, Los Angeles. Thursday-Sunday. Contact: John S. McDonald, MD, Dept. of Anesthesiology, OSU, 410 W. 10th Ave., Columbus, OH 43210. (614) 422-5591.

February 13—**Local Anesthesia and Regional Blocks.** See Emergency Medicine, February 13.

March 30-April 5—**Obstetric Anesthesia.** Ohio State University, Dept. of Anesthesiology, at Sheraton Waikiki Hotel, Oahu, Hawaii. One week. Contact: John S. McDonald, MD, Dept. of Anesthesiology, OSU, 410 W. 10th Ave., Columbus, OH 43210. (614) 422-5591.

CANCER

December 12—**15th Annual Northern California Cancer Conference.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 7 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Memorial Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 284.

January 7—**The Unknown Primary.** San Joaquin Community Hospital, Bakersfield. Monday. 1 hr. Contact: Oncology Services, San Joaquin Com. Hosp., 2615 Eye St., Bakersfield 93301. (805) 327-1711, ext. 363.

January 16—**Testicular Tumors.** Hospital of the Good Samaritan at Bonaventure, Los Angeles. Wednesday. Contact: Janie Sternal, Cont. Med. Ed., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

January 19—**Advances, Treatments and Modern Techniques in Leukemia.** S.F. Regional Cancer Foundation and Leukemia Soc. of America at Fireman's Fund Bldg., San Francisco. Saturday. Contact: Dr. Terry Sheehy, S.F. Reg. Cancer Fndn., 14th and Lake, San Francisco 94118. (415) 211-2132.

January 25-26—**Cancer Update.** Peralta Hospital at Claremont Hotel, Berkeley. Friday-Saturday. 10 hrs. Contact: Education and Training Dept., Peralta Hosp., 450 30th St., Oakland 94609. (415) 451-4900.

February 1-3—**Living with Childhood Cancer.** UCSD at Bahia Hotel, San Diego. Friday-Sunday. 14 hrs. $90.

February 23—**Current Trends in Lung Cancer Diagnosis and Management—6th Annual Pulmonary Symposium.** USC and Inter-Community Hosp., Covina, at Calif. State Univ., Pomona. Saturday. 6 hrs. Contact: Linda Arbiter, MPH, Med. Ed. Coordinator, Inter-Community Hosp., 303 N. 3rd Ave., Covina 91723.

March 14—**Cancer of the Endometrium.** California Hospital Medical Center, Los Angeles. Friday. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411, ext. 251.

March 15-16—**Pharmaceutical Aspects of Cancer Care—15th Annual San Francisco Cancer Symposium.** West Coast Cancer Foundation and American Cancer Soc. at Hyatt on Union Square, San Francisco. Saturday-Sunday. Contact: West Coast Cancer Foundation, 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

EMERGENCY MEDICINE

November 30-December 1—**Emergency Medicine.** UCLA at Miramar-Sheraton, Santa Monica. Friday-Saturday. 13½ hrs. $160.

December 6-8—**Trauma.** See Surgery, December 6-8.

December 6-8—**Hand and Wrist Trauma.** See Surgery, December 6-8.

December 10-14—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $350.

December 14-16—**Critical Care Medicine: Taking Stock of Shock.** See Of Interest To All, December 14-16.

December 15—**Physical Assessment and Diagnosis Course for Emergency and Primary Care Physicians.** Memorial Hospital Medical Center, Long Beach. Saturday. 6 hrs. $65. Contact: Program Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

January 8—**CAT Scan and Ultrasound in Emergency Medicine.** Cottage Hospital and Assn. of Emergency Physicians for

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Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Lolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

Ventura and Santa Barbara Counties at Cottage Hosp., Santa Barbara. Tuesday; 8:00 p.m. 1½ hrs. CMA and ACEP. Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

January 14-18—**Medical Management of EMS Systems.** UCSD at Hilton, San Diego, Monday-Friday. 36 hrs.

January 21-25—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

January 21-25—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

February 10-15—**Emergency Medicine 1980.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

February 11-15—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

February 13—**Local Anesthesia and Regional Blocks.** Los Robles Hosp. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at Los Robles Reg. Med. Ctr., Thousand Oaks. Wednesday; 8:00 p.m. 1½ hrs. CMA and ACEP. Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

February 14-15—**Maxillofacial Trauma.** See Surgery, February 14-15.

March 9-15—**Mammoth Mountain Emergency Medicine Ski Conference.** UCI and Orange Co. Emergency Dept. Nurses' Assn. at Mammoth Lakes. Sunday-Saturday. 24 hrs. Cat. I CMA, ACEP; 24 elective credit hrs. AAFP. $250. Contact: Daniel Abbott, MD, Med. Conf., Inc., P.O. Box 52-B, Newport Beach 92662. (714) 642-7080.

March 17-21—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

MEDICINE

November 15-16—**Neurology Update.** UCSD at Vacation Village, San Diego. Thursday-Friday.

November 15-17—**Advanced Cardiopulmonary Care.** PMC at Holiday Inn-Financial District/Presbyterian Hospital, San Francisco. Thursday-Saturday. 12 hrs. lecture; 18 hrs. lecture and workshop. $150 for lecture; $235, lecture and workshop.

November 18—**Advances in Cardiovascular Disease.** Granada Hills Community Hosp. at Sheraton Universal Hotel, North Hollywood. Sunday. Contact: Germaine Thrasher, Symp. Sec., Granada Hills 91344. (213) 360-1021.

November 30—**The Problems of Essential Hypertension in the 1980's.** UCD at Red Lion Motor Inn, Sacramento. Friday. 7 hrs. $25.

November 30-December 1—**Practical Endocrinology for Primary Care Physicians.** UCLA. Friday-Saturday.

November 30-December 2—**Concepts of Common Infectious Diseases.** UCSD at Hilton, San Diego. Friday-Sunday. 15 hrs. $175.

December 5—**Viral Hepatitis.** USC. Wed.

December 6-7—**5th Annual Lyman A. Brewer, III, Cardiothoracic Symposium—The Esophagus.** White Memorial Medical Center at Bonaventure Hotel, Los Angeles. Thursday-Friday. Contact: Dir., Dept. of CME, White Memorial Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 263-6100 or (213) 268-5000.

December 6-9—**Neurotology Workshop.** PMC at Ilikai Hotel, Honolulu. Thursday-Sunday. 24 hrs. $435.

December 7-8—**Allergy/Immunology, Infectious Diseases, Endocrinology/Metabolism, Oncology.** American College of Physicians at San Francisco. Friday-Saturday. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200.

December 7-9—**Advances in Heart Disease 1980—12th Annual Seminar on Clinical Cardiology.** American College of Cardiology at Fairmont Hotel, San Francisco. Friday-Sunday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

December 12—**Management of Hypertension.** LLU. Wednesday. 4 hrs.

January 6-13—**Echocardiography in Hawaii.** Honolulu Medical Group Research and Education Foundation, Univ. of Hawaii School of Medicine, Univ. of Rochester School of Medicine at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 18 hrs. Contact: Echocardiography in Hawaii, Honolulu Med. Grp. Research and Ed. Fnd., 550 S. Beretania St., Honolulu 96813. (808) 537-2211.

January 8-12—**Intensive Review of Common Allergic and Asthmatic Diseases.** UCD at Inter-Continental Hotel, Maui, Hawaii. Tuesday-Saturday. 25 hrs. $250.

January 9—**Dermatology Symposium.** N. T. Enloe Memorial Hosp. at Holiday Inn, Chico. Wednesday. 6 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Mem. Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102.

January 9-March 12—**Pulmonary Diseases for the Practicing Internist.** UCLA. Wednesday evenings. 20 hrs.

January 20-24—**Angiography and Vascular Disease.** UCSD at Vacation Village, San Diego. Sunday-Thursday. 26 hrs. $325.

January 26-27—**The Healing Brain.** UCSF Cont. Ed. Health Sciences and Institute for the Study of Human Knowledge at Sheraton-Palace, San Francisco. Saturday-Sunday. Contact: UCSF, Cont. Ed. Health Sciences, 1308 3rd Ave., San Francisco 94143. (415) 666-2894.

January 26-February 2—**Nephrology.** USC at Princeville at Hanalei, Kauai, Hawaii. One week.

January 31-February 1—**Hypertension: Advances in Treatment.** American Heart Assn., Orange Co. Chap., at Registry Hotel, Irvine. Thursday-Friday. Contact: AHA, Orange Co. Chap., 1043 Civic Center Dr. West, Santa Ana 92703. (714) 547-3001.

January 31-February 2—**Fundamentals of Echocardiography—An Introductory Course for Clinicians.** American College of Cardiology at Century Plaza, Los Angeles. Thursday-Saturday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 1-3—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Bahia Hotel, San Diego. Friday-Sunday. 13 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

February 2—**Pediatric Dermatology Seminar.** STAN. Saturday. Contact: Paul H. Jacobs, MD, Dept. of Derm., Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

February 7-9—**Tri-State Symposium on Clinical Cardiology.** American Heart Assn.'s Council on Clinical Cardiology; AHA, Greater Los Angeles, Arizona and New Mexico Affiliates, at Disneyland Hotel, Anaheim. Thursday-Saturday. 15 hrs. $200, Heart Assn. member; $250, nonmember. Contact: LaVerna Titus, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

February 13—**Chronic Obstructive Pulmonary Disease.** LLU. Wednesday. 4 hrs.

February 13-15—**Advances in Neurology.** UCSF. Wednesday-Friday.

February 13-15—**Cardiovascular Disease—1980: Advances in Diagnosis and Management.** American College of Cardiology at Vacation Village, San Diego. Wednesday-Friday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 16—**5th Annual Liver Conference, Cholestasis.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 7 hrs. $105. Contact: Prog. Coord., Ctr. for Health Ed., 2801 Atlantic Ave, Long Beach 90801. (213) 595-3811.

February 16-17—**Practical Gastroenterology for Primary Care Physicians.** UCLA. Saturday-Sunday. 12 hrs. $160.

February 21-24—**Federation of Western Societies of Neurological Science—Annual Meeting.** Biltmore Hotel, Santa Barbara. Thursday-Sunday. Contact: J. Carroll Ramseyer, MD, EEG/EMG Laboratory, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017.

February 22-23—**Medical Knowledge Self Assessment II.** American College of Physicians and PMC at Hyatt Regency, San Francisco. Friday-Saturday. 12 hrs. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

February 22-23—**Rehabilitation in Neurological Dysfunction.** PMC at Mark Hopkins Hotel, San Francisco. Friday-Saturday. 9 hrs. $135.

March 7—**6th Annual Diabetes Program.** UCD at Red Lion Motor Inn, Sacramento. Friday. 6½ hrs.

March 7-9—**Northern California-Nevada Regional Meeting, American College of Physicians.** Doubletree Inn, Monterey. Friday-Sunday. Contact: Ralph O. Wallerstein, MD, 3838 California St., San Francisco 94118.

March 14-16—**Pediatric Cardiology—A Growing Concern: What the Primary Care Physician Should Know.** UCD at Hyatt Lake Tahoe, Incline Village. Friday-Sunday. 15 hrs.

March 15-16—**Human Lymphocyte Antigens.** UCSD at Hilton, San Diego. Saturday-Sunday.

March 16-19—**Basic Cardiology for the Primary Care Physician.** UCSF at Yosemite. Sunday-Wednesday.

March 21-23—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Jack Tar Hotel, San Francisco. Friday-Sunday. 15 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

March 24-26—**4th Annual Review and Update of the Immunology and Clinical Practice of Allergy.** USCD at Hilton, San Diego. Monday-Wednesday. 20 hrs. $210.

March 24-April 4—**Intensive Review of Internal Medicine.** USC. Two weeks.

March 26-28—**Endocrine Glands in Health and Disease.** UCSF at Golden Gateway Holiday Inn, San Francisco. Wednesday-Friday.

March 29-April 5—**Infectious Diseases.** Univ. of Washington School of Medicine at Naniloa and Kona Surf Hotels, Hilo, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

OBSTETRICS AND GYNECOLOGY

November 29-December 1—**Controversies in Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Canyon Hotel, Palm Springs. Thursday-Saturday. 18 hrs. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 6-9—**Gynecologic Urology: Theory and Practice, Basic and Advanced.** Memorial Hospital Medical Center-UCI Center for Health Education at Sheraton-Universal, Hollywood. Thursday-Sunday. 20 hrs. $325. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 7-8—**Adolescent Sexuality and Gynecology.** PMC. Friday-Saturday. 9 hrs. $125.

January 12-19—**Perinatal Medicine.** USC at Royal Lahaina, Maui, Hawaii. One week.

January 20-23—**Obstetrics-Gynecology Update.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Wednesday. 20 hrs.

January 21-25—**Ob/Gyn Review.** USC. Monday-Friday.

January 23-26—**Clinical Obstetrics and Gynecology and Histological Pathology.** UCI and Women's Hospital of Long Beach at Newporter Inn, Newport Beach. Wednesday-Saturday. 26 hrs. $250. Contact: Prog. Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801.

February 9-10—**Obstetrical and Gynecological Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton, Beverly Hills. Saturday-Sunday. 10 hrs. $70. Contact: Miss Dee Davis, Exec. Sec., 5820 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

March 12—**Vaginitis.** LLU. Wednesday. 4 hrs.

March 22-23—**Contraception: Current Research and Multidisciplinary Applications.** See Of Interest To All, March 22-23.

PEDIATRICS

November 16—**Phil Rothman Memorial Lecture.** Childrens Hospital of Los Angeles. Friday. Contact: Robert Romans, MD, Cont. Med. Ed., Childrens Hosp., P.O. Box 54700, Terminal Annex, Los Angeles 90054. (213) 669-2518.

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28 Hours
Category I Credit

November 16-19—**Las Vegas Seminars.** American Academy of Pediatrics, Calif. Chapters 1, 2, 3, at Hilton Hotel, Las Vegas. Friday-Monday. $175, members; $200, nonmembers. Contact: AAP, Chap. 2, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

November 26-29—**Developmentally Disabled Child.** UCSD at Vacation Village, San Diego. Monday-Thursday.

December 6-8—**Pediatric Allergy/Immunology.** UCSF. Thursday-Saturday.

February 2—**Pediatric Dermatology Seminar.** See Medicine, February 2.

February 4-6—**Pediatric Nephrology and Urology.** UCSD at Vacation Village, San Diego. Monday-Wednesday.

February 7-10—**7th Neonatal and Infant Respiratory Symposium.** See Anesthesiology, February 7-10.

February 9-10—**The Health of the Young and the Development of Sexuality and Gender.** UCSF Cont. Ed. Health Sciences at Sheraton-Palace, San Francisco. Saturday-Sunday. Contact: UCSF, Cont. Ed. Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

February 23—**Pediatric Review.** UCLA. Saturday.

March 5-7—**Pediatric Pulmonary Symposium.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

March 8—**Adolescent Medicine.** UCLA. Saturday.

March 14-16—**Pediatric Cardiology.** See Medicine, March 14-16.

PSYCHIATRY

November 16—**Interviewing Skills in Psychiatry.** PMC at San Diego. Friday. 4 hrs. $25.

November 26-30—**Group Therapy Seminars.** UCSF at VA Hospital, Oakland. Monday-Friday. 31 hrs. $50.

December 14—**Interviewing Skills in Psychiatry.** PMC at Anaheim. Friday. 4 hrs. $25.

January 12—**Neuroregulators and Brain Function.** No. Calif. Psychiatric Assn. and McAuley Institute at St. Mary's Hosp., San Francisco. Saturday. 3 hrs. Contact: George L. Ponomareff, MD, 2457 Grove Way, Suite 102, Hayward 94546.

January 18-20—**Brief Psychotherapy.** UCSF. Friday-Sunday.

January 26-27—**The Healing Brain.** See Medicine, January 26-27.

January 27-February 1—**Midwinter Program in Continuing Education for Psychiatrists—6th Annual.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday. 26 hrs. $200.

February 6-9—**Update in Psychiatry: Psychopharmacology.** UCSD at Vacation Village, San Diego. Wednesday-Saturday. 16 hrs. $200.

February 9—**Childhood Experiences and Adult Behavior.** No. Calif. Psychiatric Assn. and McAuley Institute at St. Mary's Hosp., San Francisco. Saturday. 3 hrs. Contact: George L. Ponomareff, MD, 2457 Grove Way, Suite 102, Hayward 94546.

February 9-10—**Sexual Therapy.** UCLA. Saturday-Sunday.

March 21-23—**Narcissism—A Multidimensional View.** UCSF. Friday-Sunday.

RADIOLOGY AND PATHOLOGY

December 13—**Bone and Joint Clinical-Pathological-Radiological Correlation Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 9—**Gastrointestinal Radiology and Diagnosis.** LLU. Wednesday. 4 hrs.

January 10—**Bone and Joint Clinical-Pathological-Radiological Correlation Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 23-25—**7th Annual Genitourinary Pathology Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 23-26—**Clinical Obstetrics and Gynecology and Histological Pathology.** See Obstetrics and Gynecology, January 23-26.

January 25-27—**32nd Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Nathan Green, MD, 15107 Vanowen St., Van Nuys 91405.

January 26-27—**Modern Gastrointestinal Radiologic Techniques for Practicing Physicians.** UCSF at Fairmont, San Francisco. Saturday-Sunday. 13 hrs. $200.

January 28-February 1—**Computed Tomography, Ultrasound and X-Ray—An Integrated Approach.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. 32 hrs. $295.

January 30-February 1—**Genito-Urinary Pathology—7th Annual Course.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 22½ hrs. $220. Contact: Prog. Coord., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 1-3—**Neuroradiology.** UCSF at Fairmont, San Francisco. Friday-Sunday. 20 hrs. $190.

February 14—**Bone and Joint Clinical-Pathological-Radiological Correlation Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 22—**Practical Laboratory Mycobacteriology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 27-29—**Sierra Radiology Conference—Radiology of Problems in Clinical Medicine.** Sacramento Radiology Research and Education Foundation and Northern Calif. Radiological Society at Sahara Tahoe Hotel, South Lake Tahoe. Wednesday-Friday. 18 hrs. $215. Contact: Michael H. Reid, PhD, MD, Prog. Dir., Sacramento Radiology Research and Education Foundation, P.O. Box 161112, Sacramento 95816.

March 1-2—**Concepts and Controversies in Cardiopulmonary Imaging.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday. 11 hrs. $150.

March 3-7—**Diagnostic Radiology.** UCSF. Monday-Friday.

March 8-9—**A Practical Course in B-Scan Ultrasound.** UCSF. Saturday-Sunday.

March 13—**Bone and Joint Clinical-Pathological-Radiological Correlation Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 23 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

November 24-December 1—**International Seminar on Operative Arthroscopy.** UCLA at Kauai, Hawaii. One week. 39 hrs. $650, with laboratories; $450 without laboratories.

December 6-8—**Trauma.** No. Calif. Chap. Committee on Trauma of the American College of Surgeons at Claremont Resort Hotel, Oakland. Thursday-Saturday. Contact: F. William Blaisdell, MD, Dept. of Surg., UCD Sch. of Med., Rm. 257, 4301 X St., Sacramento 95817. (916) 453-2207.

December 6-8—**Hand and Wrist Trauma.** The Bone and Joint Disease Foundation at San Diego. Thursday-Saturday. Contact: The Bone and Joint Disease Foundation, P.O. Box 82441, San Diego 92138.

December 6-9—**Gynecologic Urology.** See Obstetrics and Gynecology, December 6-9.

December 6-9—**Neurotology Workshop.** PMC at Ilikai Hotel, Honolulu. Thursday-Sunday. 24 hrs. $435.

December 7—**Course in Flexible Fiberoptic Sigmoidoscopy.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 8—**Blepharoplasty and Other Cosmetic Surgery of the Eyelid.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

January 14-18—**Otologic Surgery Course—15th Annual.** Ear Research Institute, Los Angeles. Monday-Friday. 40 hrs. $500. Contact F. H. Linthicum, Jr., MD, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

January 18-19—**2nd Annual Postgraduate Course in Surgery.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 12 hrs.

January 21-24—**Assembly in Surgery.** UCSD at Islandia Hyatt House, San Diego. Monday-Thursday. 28 hrs.

January 22-June 14—**Recent Advances in Surgical Science.** UCLA at Wadsworth VA Hospital, Los Angeles. One evening/month.

January 27-30—**21st Annual Theodor Billroth Course in Surgical Anatomy.** LLU. Sunday-Wednesday. 32 hrs. $250.

January 31-February 2—**Calculi.** American Urological Assn. at San Francisco. Wednesday-Friday. Contact: Office of Education, AUA, P.O. Box 1129, Aspen, CO 81611. (303) 925-2018.

February 6-8—**Annual Ophthalmology Course.** UCSF. Wednesday-Friday.

February 7-9—**Vascular Surgery.** UCSF. Thursday-Saturday.

February 8-9—**Cataract Surgery and Intraocular Lenses: Planned Extracapsular, Phacoemulsification and Intracapsular Techniques.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $450. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

February 14-15—**Maxillofacial Trauma.** UCSF at Fairmont Hotel, San Francisco. Thursday-Friday. 15 hrs. $200.

March 1—**Corneal-External Ocular Disease Surgery Course.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $225. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

March 7-8—**Ophthalmology Update.** UCD, PMC, UCSF, STAN. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

March 15-19—**Controversial Areas in Surgery—17th Annual Seminar.** UCLA at Canyon Hotel, Palm Springs. Saturday-Wednesday.

March 18-21—**Basic Science for Surgeons.** STAN at The Lodge, Pebble Beach. Tuesday-Friday.

March 19-23—**Vascular Surgery—8th Annual Symposium.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday.

March 25-29—**3rd U.S. Intraocular Lens Symposium and 7th Scientific Session.** American Intra-Ocular Implant Society at Century Plaza Hotel, Los Angeles. Tuesday-Saturday. 30 hrs. Contact: Debbi Miller, Dir. of Mtg. Services, AIOIS, P.O. Box 3140, Santa Monica 90403. (213) 395-3937.

OF INTEREST TO ALL PHYSICIANS

November 16-17—**Nutrition in Your Daily Practice.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 17-18—**Third Annual Symposium on Aging.** UCSF. Saturday-Sunday. Contact: UCSF, Cont. Ed. Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

November 26-30—**Postgraduate Institute for Primary Care Physicians.** UCSD at Hilton Hotel, San Diego. Monday-Friday. 40 hrs.

November 30—**The Many Faces of Shock—1979.** Daniel Free-

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man Hospital at Hyatt House, Los Angeles. Friday. 6 hrs. $90. Contact: Donald A. Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Hosp., 333 N. Prairie Ave., Inglewood 90301. (213) 674-7050.

November 30-December 2—**Physicians—Stress and Coping.** CMA and UCD at Greenwood Lodge, Soquel. Friday-Sunday. 7 hrs. $75/person; $125/couple. Contact: Gail Jara, CMA.

December 1-2—**Human Sexuality and the Treatment of Sexual Dysfunction.** USC. Saturday-Sunday.

December 1-2—**Sports Medicine Conference—9th Annual.** UCSF. Saturday-Sunday.

December 5-7—**Prevention in Primary Care.** UCSD at Vacation Village, San Diego. 20 hrs. $200.

December 9-11—**Metabolic and Nutritional Care.** UCSF at Fairmont Hotel, San Francisco. Sunday-Tuesday. 18 hrs.

December 14-16—**Critical Care Medicine: Taking Stock of Shock.** Medical Education Foundation of Santa Barbara County at Alisal Guest Ranch, Solvang. Friday-Sunday. 8 hrs. $65, members; $75, nonmembers. Contact: Tara Brown, MEF, 9 E. Pedregosa, Santa Barbara 93101. (805) 965-5275.

December 15—**Physical Assessment and Diagnosis Course for Emergency and Primary Care Physicians.** See Emergency Medicine, December 15.

January 8-March 25—**Acupuncture, Acupressure and Transcutaneous Nerve Stimulation for Pain Control.** UCLA. Tuesday evenings. 58 hrs. $500.

January 12-13—**Current Drugs and Their Usage.** UCLA. Saturday-Sunday. 11 hrs. $150.

January 21-25—**Therapy: Principles and Use of Drugs.** STAN at Hyatt on Union Square, San Francisco. Monday-Friday. 25 hrs. $290.

January 30-February 2—**Primary Care: Current Management of Common Office Problems.** UCSF. Wednesday-Friday.

January 31-February 2—**Medical and Legal Aspects of Asbestosis.** USC. Thursday-Saturday.

February 1-7—**LLU Alumni Association—48th Annual Postgraduate Convention.** One week.

February 4-9—**Family Practice Refresher Course—11th Annual.** UCI at Marriott Inn, Newport Beach. Monday-Saturday.

February 5-June 24—**Family Practice Review.** USC. Tuesday evenings.

February 8-13—**California Medical Association—109th Annual Session.** Town and Country, San Diego. Friday-Wednesday. Contact: Rocki Lai, CMA.

February 9-10—**Sexual Therapy.** See Psychiatry, February 9-10.

February 10-13—**Medical Evaluation of the Preoperative Patient.** UCD at Hyatt Lake Tahoe, Incline Village. 15½ hrs. $135.

February 13—**Environmental Medicine.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 6 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Mem. Mosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 283.

February 14-15—**Management of the Ventilator Dependent Patient.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. 14 hrs. Contact: Prog. Coord., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 15-16—**Health Care and the Changing Society.** Vista Hill Foundation and Mesa Vista Hosp. at Hotel del Coronado, Coronado. Friday-Saturday. 9 hrs. Contact: Virginia Everett, Vista Hill Foundation, 3420 Camino del Rio, Suite 100, San Diego 92108. (714) 563-1770.

February 21-22—**New and Old Antibiotics.** USC. Thursday-Friday.

February 23-24—**Health in the Workplace.** UCSF Cont. Ed. Health Sciences. Saturday-Sunday. Contact: UCSF, Cont. Ed. Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

February 24-26—**Neurology for Non-Neurologists.** UCSD at Hilton, San Diego. Sunday-Tuesday. 21 hrs. $250.

February 25-29—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $290.

February 26-March 2—**Critical Care Medicine.** USC at Hilton, San Francisco. Tuesday-Sunday.

February 27—**Hospital Infection Control.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday. 7 hrs. Contact: Prog. Coord., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

March 1-2—**Genetic Disorders.** UCLA. Saturday-Sunday.

March 5-April 23—**General Preventive Medicine.** USC. Wednesday evenings.

March 9-15—**Critical Care II and Ski.** College of Medical Education, Pierce Co. (WA) Med. Soc. at Sahara Lake Tahoe, Incline Village. One week. Contact: Maxine Bailey, College of Med. Ed., Pierce Co. Med. Soc., 705 S. 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

March 9-16—**Sports Medicine.** Center for Sports Medicine, Northwestern Univ. Med. Sch.; Div. of Sports Med., No. Carolina Dept. of Public Instruction at Intercontinental Hotel, Maui, Hawaii. One week. Contact: Marianne Porter, Ctr. for Sports Med., 2-063, 303 E. Chicago Ave., Chicago 60611.

March 12—**Refresher in Family Practice.** N. T. Enloe Memorial Hosp. at Holiday Inn, Chico. Wednesday. 6 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Mem. Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 283.

March 15—**Medical Treatment of Alcoholism.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7 hrs.

March 15-16—**Practical ENT for Primary Care Physicians.** UCLA. Saturday-Sunday.

March 15-16—**Human Lymphocyte Antigens.** See Medicine, March 15-16.

March 15, 29—**Placebos: The Power of Positive Expectant Faith.** UCLA. 2 Saturdays.

March 18-22—**Sports Medicine.** University of Hawaii School of Medicine at Princess Kaiulani Hotel, Waikiki, Honolulu, Hawaii. Tuesday-Saturday. 18 hrs. $200. Contact: Hawaii Conference Services, P.O. Box 25055, Honolulu 96825. (808) 377-6445.

March 22-23—**Contraception: Current Research and Multidisciplinary Applications.** UCSF. Saturday-Sunday. Contact: UCSF, Cont. Ed. Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

March 24-28—**Postgraduate Institute for Primary Care Physicians.** UCSD at Vacation Village, San Diego. Monday-Friday.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD Douglas Community Hospital, 738 West Harvard Avenue Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland, OR 97227. (503) 280-3200.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

February 11-15—**Eleventh Annual Family Practice Review.** Portland, Monday-Friday. Hilton Hotel. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

SURGERY

December 7-8—**Advances and Controversies in Surgical Oncology.** Portland, Friday-Saturday. Hilton Hotel. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OF INTEREST TO ALL PHYSICIANS

November 16-17—**Sixth Annual Symposium on Critical Care Medicine.** Portland, Friday-Saturday. Jantzen Beach Red Lion. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 16-20—**American College of Physicians Review Course.** Portland, Monday-Friday. Jantzen Beach Thunderbird. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 25-27—**Symposium on Sports Medicine.** Eugene, Wednesday-Friday. Thunderbird Motor Inn. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

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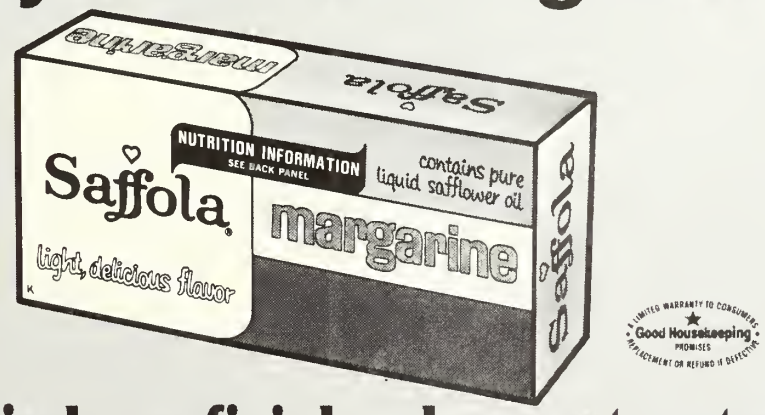

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WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

November 15-16—**Critically Ill Surgical Patient.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

November 15-17—**Pearls in Primary and Emergent Care.** Seattle. Thursday-Saturday. Washington Plaza Hotel. Contact: Marilyn Carlson, Northwest Hospital, 1551 North 120th, Seattle, WA 98133. (206) 364-0500, ext. 686.

November 17-24—**Tax Estate and Financial Planning.** Kauai, Hawaii. Saturday thru Saturday. Kauai Surf. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

November 28—**Endocrinology Circuit Course.** Spokane. Wednesday (4 hours). Sacred Heart Medical Center, Spokane. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

November 30, December 1—**Aging and the Elderly.** Seattle. Friday-Saturday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

December 1-2—**Dynamics of Patient-Physician Relationships.** Seattle. Saturday-Sunday. 6th Floor, Group Health Cooperative of Puget Sound. Contact: Office of Education, Group Health, A-5, 201 16th Ave., E., Seattle, WA 98112. (206) 326-7348.

December 6-7—**American College of Physicians Medical Knowledge Self-Assessment Program V (MKSAP V).** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

December 6—**Behavioral Methods in Pain Management.** Seattle. Thursday. Swedish Hospital Auditorium. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

December 7—**Biofeedback.** Seattle. Friday. Swedish Hospital Auditorium. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

December 14-15—**Orthopedics for the Family Physician.** Seattle. Friday-Saturday. Swedish Hospital and Medical Center. Contact: John L. Wright, MD, Swedish Hospital and Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2265.

January 8, 10, 12—**The Geriatric Patient.** Tacoma. Tuesday, Thursday, Saturday. Puget Sound Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 S. 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

January 12—**Conference on Obstetrics and Gynecology.** Seattle. Saturday. Providence Medical Center. Contact: Evelyn Foote, Continuing Education, Providence Medical Center, 500 17th Ave., Seattle, WA 98122. (206) 326-5821.

January 17-18—**Pediatric Update.** Seattle. Thursday-Friday. Children's Orthopedic Hospital and Medical Center. Contact: UW School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

January 23-February 1—**Critical Care I and Ski.** Val Gardenia, Italian Alps. Ten Days. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

January 26—**Radiology Above the Belt.** Seattle. Saturday. 6th Floor, Group Health Cooperative of Puget Sound. Contact: Office of Education, Group Health, A-5, 201 16th Ave., E., Seattle, WA 98112. (206) 326-7348.

January 26—**Rheumatology.** Tacoma. Saturday. St. Joseph Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

January 29-30—**Tax Estate and Financial Planning.** Seattle. Tuesday-Wednesday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

January 31, February 1-2—**Neuro-ophthalmology—Annual President's Meeting.** Seattle. Thursday-Saturday. Olympic Hotel. Contact: Marcia Wahlman, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Room 900, Seattle, WA 98121. (206) 623-4801.

February 1-2—**Violence in the Family.** Seattle. Friday-Saturday. Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 9-16—**Sun Valley Critical Care: Maternal/Perinatal.** Sun Valley, Idaho. Saturday thru Saturday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 14-15—**Advances in Neurology: Headaches.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 15—**Peripheral Vascular Disease.** Tacoma. Friday. Tacoma General Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

February 18—**Endocrinology Circuit Course.** Vancouver, WA. Monday (4 hours). St. Joseph Community Hospital. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 19—**Endocrinology Circuit Course.** Longview. Tuesday (4 hours). Monticello Medical Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 20—**Endocrinology Circuit Course.** Olympia. Wednesday (4 hours). Tyee Motor Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 21—**Endocrinology Circuit Course.** Bremerton. Thursday. Harrison Memorial Hospital. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 22—**Endocrinology Circuit Course.** Bellingham. Friday. Western Washington University. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 23-March 1—**Office Orthopedics for Primary Physicians.** Sun Valley, Idaho. Saturday-Saturday. Sun Valley Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 28-29—**Northwest Stroke Symposium.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: Education and Training Department, Northwest Hospital, 1551 North 120th, Seattle, WA 98133. (206) 364-0500, ext. 686.

March 6-7—**American College of Physicians Medical Knowledge Self-Assessment Program V (MKSAP V).** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 8-15—**Psychiatry for Primary Physicians.** Sun Valley, Idaho. Saturday-Saturday. Sun Valley Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 9-15—**Critical Care II and Ski.** Lake Tahoe, Nevada. Thursday-Wednesday. Sahara Tahoe. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

March 13-14—**Tacoma Academy of Internal Medicine Annual Scientific Program.** Tacoma. Thursday-Friday. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

March 15-22—**Sports Medicine.** Sun Valley, Idaho. Saturday-Saturday. Sun Valley Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 17-28—**Rehabilitation Medicine Review.** Seattle. Two weeks. University Towers Hotel. Contact: U/W School of

Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 21-22—**Days of Pediatrics.** Tacoma. Friday-Saturday. Mary Bridge Children's Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98450. (206) 627-7137.

March 24-28—**Advances in Family Practice.** Seattle. Monday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 29-April 5—**Infectious Diseases.** Hilo, Hawaii. Saturday-Saturday. Naniloa and Kona Surf Hotels. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 31-April 3—**American College of Physicians: Hematology.** Seattle. Monday-Thursday. Olympic Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 3-4—**Hazards to the Fetus.** Seattle. Thursday-Friday. Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 10-11—**Dermatology.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 10-11—**Annual Cancer Symposium—Gastrointestinal.** Seattle. Thursday-Friday. Swedish Hospital and Medical Center. Contact: John L. Wright, MD, Swedish Hospital and Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2265.

April 17-18—**Couples.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 18-19—**Tacoma Surgical Society Annual Scientific Program.** Tacoma. Friday-Saturday. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

April 24-25—**Respiratory Care.** Seattle. Thursday-Friday. Contract: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 24-25—**Review of Arrythmias.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 25-26—**Anesthesia: Low Flow States—Pathology and Treatment.** Vancouver, British Columbia. Friday-Saturday. Four Seasons Hotel. Contact: Dr. K. Turnbull, Academy of Medicine, 1807 West 10th Avenue, Vancouver, BC V6J 2A9.

May 1-2—**Controversies in Medicine.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 22-23—**Adolescent Medicine.** Seattle. Thursday-Friday. Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 5—**Medicine and the Law.** Port Ludlow. Thursday. Port Ludlow Resort. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 12-13—**Regional Anesthesia and Nerve Block.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 19-20—**Laboratory Medicine.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 26-27—**American College of Physicians Medical Knowledge Self-Assessment Program V (MKSAP V).** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 28-July 5—**Alaska Cruise—Emergency Medical Care: Trauma, Orthopedics and Surgery; Biomedical History.** 8 days. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

July 13-20—**Alaska Cruise—Emergency Medical Care: Trauma, Orthopedics and Surgery; Biomedical History.** 8 days. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

November 28—**Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

January 23—**Management of Premature Labor—Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

February 7—**Diagnosis of Organic Brain Syndrome—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 45th, Anchorage, AK 99504. (907) 274-7579.

MONTANA

November 28—**Pediatric Surgery—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

December 12—**Genetics—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

December 12-14—**ENT for Internists—Univ. of Wash. Internal Medicine Review Sessions.**

December 12, Wednesday, Great Falls. 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

December 13, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

December 14, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

January 9—**Pediatric Neurology—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

January 23-25—**Health Advice for Travelers; New Developments in Diagnosis and Therapy of Parasitic Disease—Univ. of Wash. Internal Medicine Review Sessions.**

January 23, Wednesday, Great Falls. 4:30-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

January 24, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

January 25, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

February 13—**Pediatric Arthritis-Immunology—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 20-22—**Diagnosis and Management of Bleeding Disorders—Univ. of Wash. Internal Medicine Review Sessions.**

February 20, Wednesday, Great Falls, 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 21, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

February 22, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: 1980—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 23-27, 1980, Registry Resort, Scottsdale.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: February 8-13, 1980, Town and Country, San Diego.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: 1980—date and place to be announced.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: 1980—date and place to be announced.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1980, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: 1980—date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 16-18, 1980, MGM Grand, Las Vegas.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 7-9, 1980, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Meeting: 1980—date and place to be announced.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: 1980—date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: 1980—date and place to be announced.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 23-27, 1980, Snow King Inn, Jackson.

February 23-24—**Annual Mid-Winter Meeting, Montana Academy of Dermatology.** Big Sky. Saturday-Sunday. Huntley Lodge. Contact: John R. Tkach, MD, 300 N. Willson, Bozeman, MT 59715. (406) 587-5442.

IDAHO

November 27—**Pediatric Radiology—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

December 11—**Pediatric Infectious Diseases—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

January 14—**Univ. of Wash. OB-GYN Session** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391.

January 22—**Pediatric Surgery—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

January 30-February 3—**Seminar in the Snow: A Postgraduate Course in Emergency Medicine.** Elkhorn Village, Sun Valley. Wednesday-Sunday. Contact D. Craig Dennis, MD, 897 MacArthur Blvd., San Leandro, CA 94577. (415) 632-1504.

February 9-16—**Sun Valley Critical Care: Maternal/Perinatal.** Sun Valley, Idaho. Saturday thru Saturday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 23-March 1—**Office Orthopedics for Primary Physicians.** Sun Valley. Saturday-Saturday. Sun Valley Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 26—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

March 1-8—**Current Concepts in Medicine—Good Samaritan Hospital, San Jose, California.** Sun Valley. Saturday-Saturday. Contact: Daman-Nelson Travel, 115 Mission St., San Francisco, CA 94105. (415) 982-3307.

March 8-15—**Psychiatry for Primary Physicians.** Sun Valley. Saturday-Saturday. Sun Valley Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

Index to
The Western Journal of Medicine Advertising

BANK OF AMERICA
Business Services 3
BETH ISRAEL CONFERENCE PROGRAM
1980 Winter Schedule 24
BURROUGHS WELLCOME CO.
Empirin c Codeine 14
Neosporin Ointment 17
CLASSIFIED 20, 22, 23
DOCTORS' COMPANY, THE 6
ELI LILLY AND COMPANY
Keflex 16
ENDO LABORATORIES
Percocet-5 ..... 18, 19
FIRSTMARK CAPITAL CORP. 26
HOLY CROSS HOSPITAL
New—Sleep Disorders Center 24
MERCK SHARP & DOHME
Aldoril 18
PATHOLOGY EDUCATION INCORPORATED
Review: Gastrointestinal Pathology and Hepatitis 25
PHARMACEUTICAL MANUFACTURERS ASSOCIATION 12, 13
PUREPAC PHARMACEUTICAL CO. 21
PVO INTERNATIONAL
Saffola Margarine 33
ROCHE LABORATORIES
Librax ..... 2nd Cover, 1, 2
Valium ..... 3rd and 4th Covers
SANDOZ PHARMACEUTICALS
Hydergine 15
SMITH KLINE & FRENCH LABORATORIES
Tagamet 11
STANFORD UNIVERSITY DEPT. OF MEDICINE
Recent Concepts of Rheumatology 24
SUN, DAVID C. H., MD MEMORIAL INSTITUTE
Gastroenterology for Clinicians—new directions 26
UNIVERSITY OF CALIFORNIA, SAN DIEGO
Assembly in Surgery 29
UNIVERSITY OF UTAH
Snowbird Conferences 25
UPJOHN COMPANY, THE
Motrin 7, 8, 9, 10
U.S. ARMY RECRUITING 31
UTAH OPHTHALMOLOGICAL SOCIETY
Annual Winter Meeting 25
YOSEMITE INSTITUTE
Mountain Medicine—Symposium 4 23

THE WESTERN Journal of Medicine

VOLUME 131 • NUMBER 6
DECEMBER 1979

Orthodox Medicine, Humanistic Medicine
th Care

Table of Contents on Third Page

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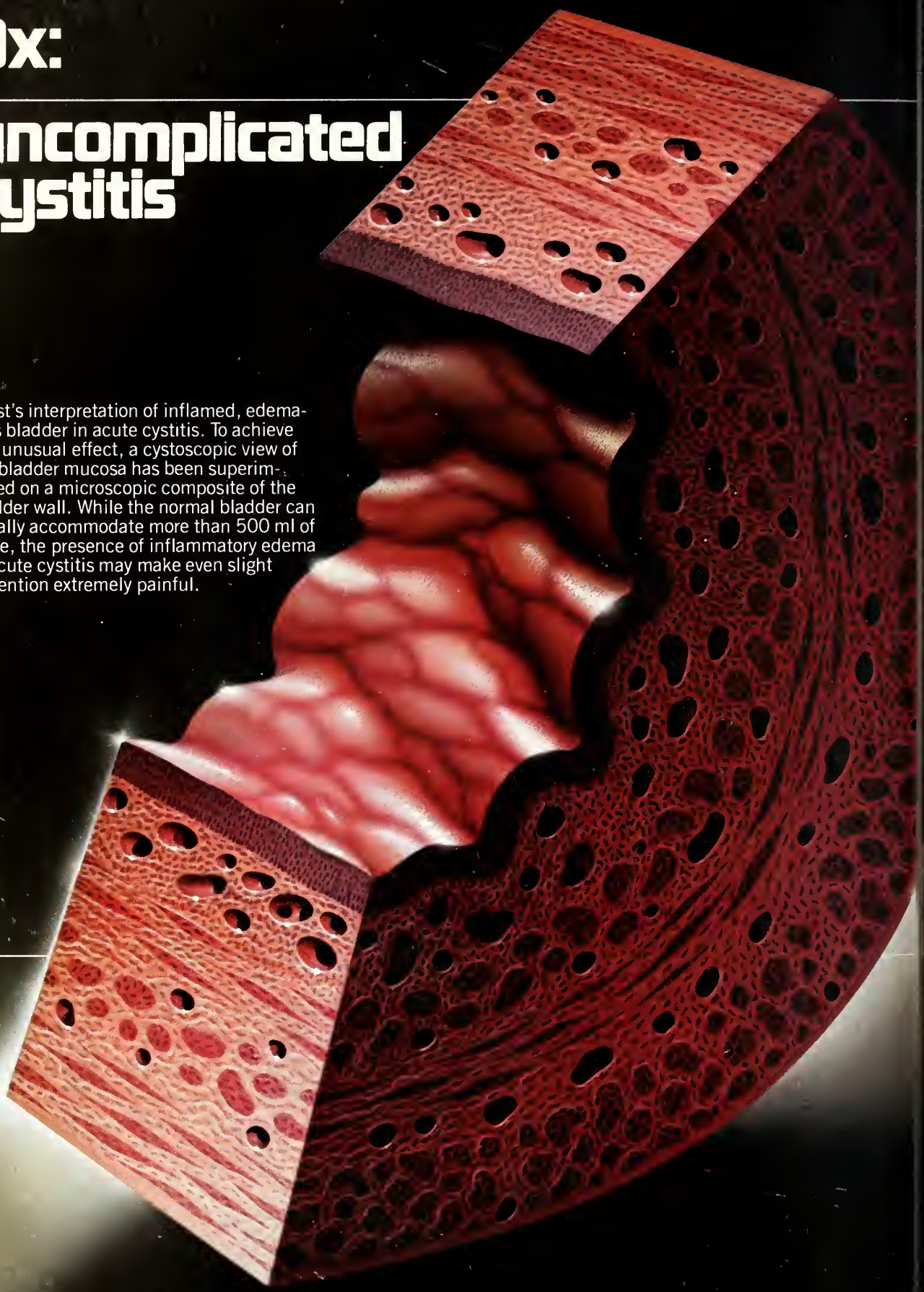

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Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma, in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

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VOLUME 131 • NUMBER 6 **DECEMBER 1979**

ORTHODOX MEDICINE, HUMANISTIC MEDICINE AND HOLISTIC HEALTH CARE

463 *Introduction* MALCOLM S. M. WATTS, MD

464 *Interface: Holistic Health and Traditional Medicine* MALCOLM C. TODD, MD

466 *Holism and Reductionism as Perspectives in Medicine and Patient Care* RICK J. CARLSON, JD

471 *What Is Health For?—Human Priorities in Health Care* JAMES VARGIU, MA, and NAOMI REMEN, MD

473 *Holistic Health and Medicine: A Challenge* LEONARD J. DUHL, MD

475 *Holistic Health: A Valuable Approach to Medical Care* MARC LAPPÉ, PhD

478 *On Healing the Whole Person: A Perspective* RICHARD H. SVIHUS, MD, DrPH

481 *Holistic Medicine: From Pathology to Prevention* KENNETH R. PELLETIER, PhD

484 *Holistic Health Care and California's Board of Medical Quality Assurance* JOHN P. BUNKER, MD, and WILLIAM G. GERBER, MD

MEDICAL PROGRESS

486 *The Clinical Physiology of Water Metabolism—Part II: Renal Mechanisms for Urinary Concentration; Diabetes Insipidus* RICHARD E. WEITZMAN, MD, and CHARLES R. KLEEMAN, MD

SPECIALTY CONFERENCE

516 *Symposium on Adolescent Gynecology and Endocrinology—Part II: Secondary Amenorrhea, Hirsutism in Adolescents and the Clinical Consequences of Stilbestrol Exposure In Utero*
Moderators: GLENN D. BRAUNSTEIN, MD, and WILLIAM D. ODELL, MD, PhD; Discussants: VAL DAVAJAN, MD; OSCAR KLETZKY, MD; GLENN D. BRAUNSTEIN, MD, and ROBERT J. KURMAN, MD
A Symposium Held at the 26th Annual Meeting of the Pacific Coast Fertility Society, Scottsdale, Arizona

MEDICAL STAFF CONFERENCE

533 *Treatment of Cardiac Arrhythmias*
Discussants: BERTRAM G. KATZUNG, MD, PhD; ROLANDO GONZALEZ, MD; MELVIN M. SCHEINMAN, MD; ARTHUR N. THOMAS, MD, and DANIEL J. ULLYOT, MD

EDITORIALS

544 • *Alternative Methods of Health Care* • *Treatment of Cardiac Arrhythmias* • *Responsibility for Health* • *Acne—Fact and Folklore*

CORRESPONDENCE

549 • *Alcohol and the Elderly* • *Inoculation by Bronchoscopy* • *Gonococcal Pharyngeal Infections; With Reply by Author*

CLINICAL REVIEW

551 *Acne* DAVID A. WHITING, MD, M Med(Derm), FRCP(Edin)

INFORMED OPINION

558 *Health Care in China—An Individual Responsibility* PAUL H. ALTROCCHI, MD, MPH, DTM

563 *Book Reviews*

566 *Volume Index*

The cover drawing is from a series of anatomical studies by Leonardo da Vinci. Most of these illustrations, now in the Royal Library at Windsor Castle, were done in Milan between 1506 and 1513, and were part of a planned definitive treatise on anatomy.

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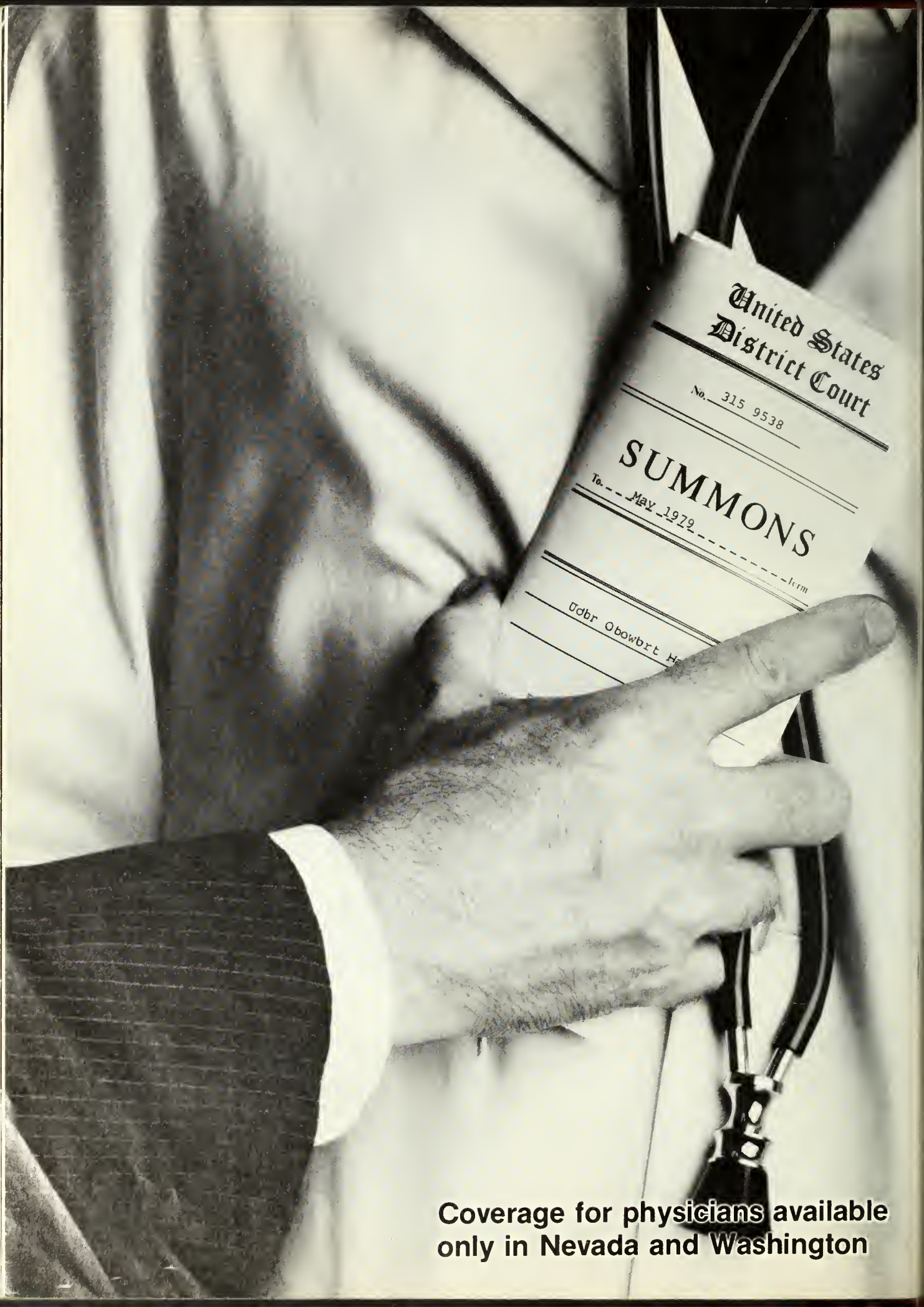

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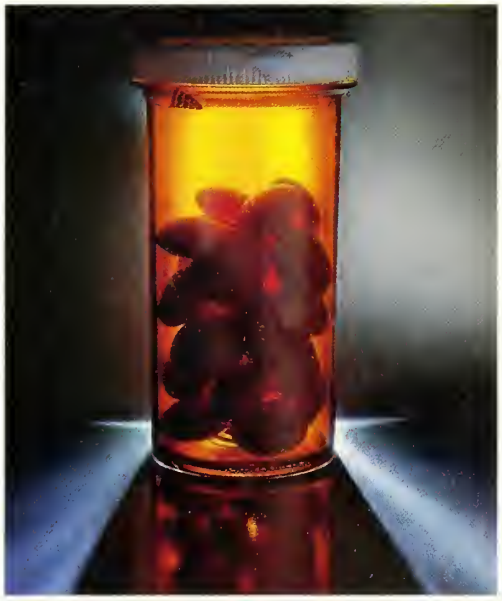

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*Incidence 3% to 9%.

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Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

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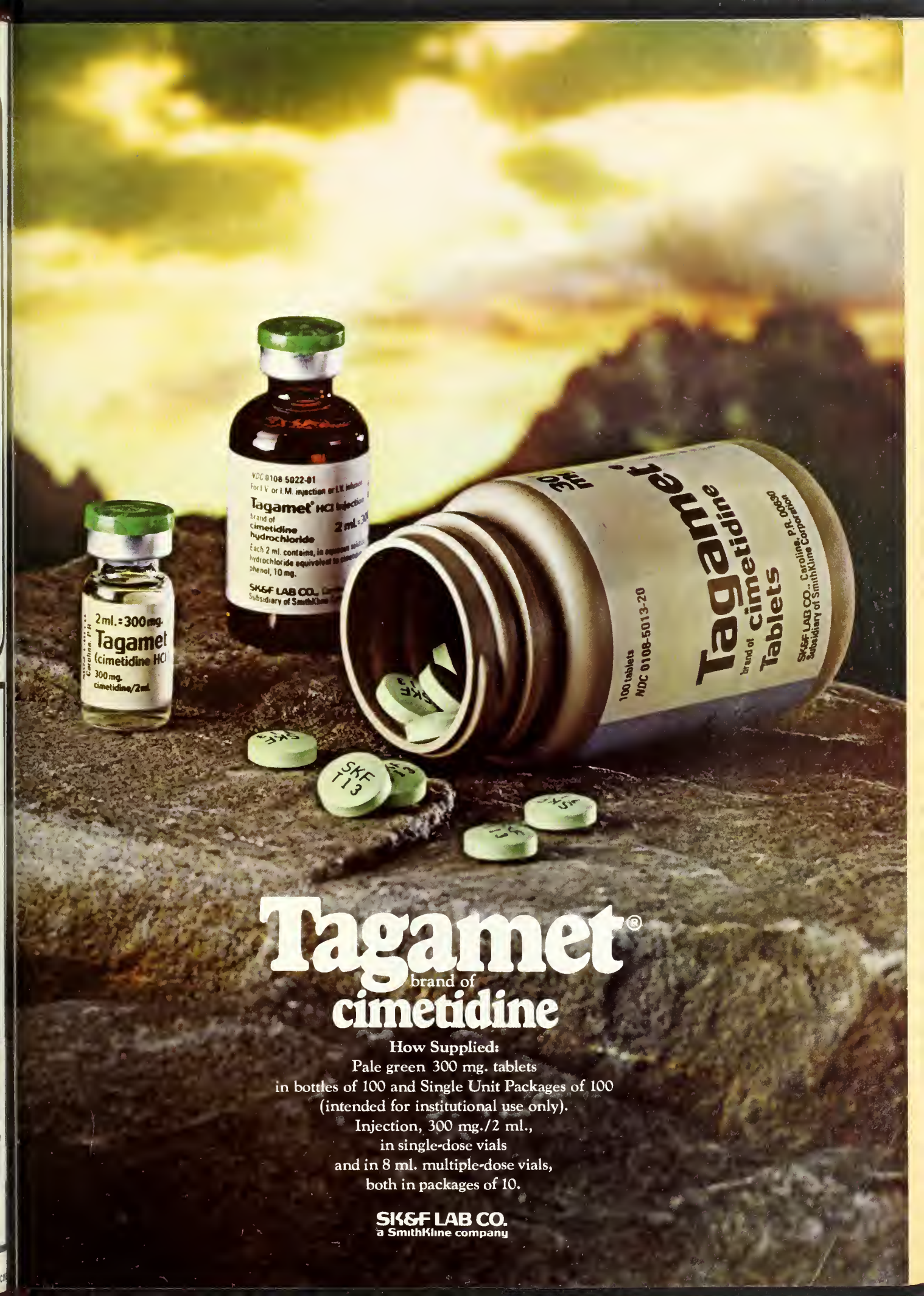
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Orthodox Medicine Humanistic Medicine Holistic Health Care

DURING THE PAST several years there has been a growing interest in what are being called humanistic medicine and holistic health care. These alternative approaches to medicine and health care are attracting adherents at a time when orthodox or *scientific* medicine is rendering more and more effective medical care than ever before. But these and other nonorthodox approaches seem to be satisfying many health care needs of many persons who either have not sought traditional care or have not been satisfied with it. It could be that traditional orthodox medicine is losing something or that there is something "out there" that physicians should be more sensitive to and know more about. It seems appropriate therefore to examine what is being called humanistic medicine and holistic health and to assess their relationships to what we call orthodox or traditional medicine.

Humanistic medicine appears to focus more upon the human or subjective side of caring and personal satisfaction, and the holistic approach emphasizes more a personal responsibility for health and the well-being of the whole person. Both employ methods not generally used in orthodox or traditional medicine, which of late has tended to be more objective and scientific as its knowledge and technical capabilities have increased.

When one reflects upon this one senses something is amiss. The idea of caring is certainly not new to orthodox medicine, nor is concern for the whole patient or health. Moreover, orthodox medicine is not all that scientific either. It too uses ritual, depends upon faith and trust, even the laying on of hands, and certainly it cannot prove the scientific worth of much that is done in accepted practice. After all, the art of medicine is by definition not scientific. Nor can orthodox medicine say that everything in the alternative approaches is worthless, particularly if there is relief and satisfaction to be gained by these means. Patients are whole persons and so are physicians and so are all other health practitioners, and there is much that is not known or understood about what makes up a whole person, let alone the ills and ailments to which the flesh is heir. There are art and science, caring and curing, illness and health, wellness and fulfillment, and poverty and deprivation. And in the prevention and care of illness there are many relationships among each and all of these.

Beginning in this issue the editors of THE WESTERN JOURNAL OF MEDICINE propose to provide a forum for dialogue and discussion of orthodox medicine, humanistic medicine and holistic health care. The forum is initiated with statements by persons known to have an interest in and knowledge of this subject. Readers are invited to submit their views constructively and succinctly. As many as space permits will be published in future issues of the journal. At an appropriate time all of the material published and unpublished, will be collated and, if possible, a distillate will be prepared to summarize the dialogue and discussion.

—MSMW

Refer to: Watts MSM (Ed): Orthodox medicine, humanistic medicine and holistic health care—A forum. West J Med 131: 463, Dec 1979

Interface: Holistic Health and Traditional Medicine

MALCOLM C. TODD, MD

It is paradoxical that at a time when contemporary medicine is providing the best quality of health care ever known, we see alternative approaches gaining greater prominence. Why do some of these apparently unorthodox alternatives become so successful? Is it patient dissatisfaction and disappointment with the doctor, or what he said, or that he does not seem to care, or that he admits "I have done all I can for Mother." Or, is there something special in these alternative approaches that our profession has overlooked?

Hardly a day passes that the postman fails to deliver two or three announcements of seminars, programs or cassettes on holistic (or wholistic) health. In September 1977 the University of Illinois held a National Symposium on Wholistic Health Care sponsored by the Kellogg Foundation and the Wholistic Health Center.[1] In December of the same year, the American Medical Association sponsored a symposium in Las Vegas on holistic medicine and health care. And in May 1978 the first American Holistic Medical Association annual session was held in Denver with Category I Continuing Medical Education credit being offered to the participants.

Thus, there seems to be a real need for the medical profession to learn what is meant by holistic health, and then to assist in establishing credibility for those procedures that have merit, while informing the public of the subjects that are products of quackery.

Finally, as we accept alternatives to health care, we should not be afraid to reject those that are not founded on a scientific basis.

Holistic comes from the Greek word *holos* which means entirety or whole. Holistic health has been defined as a state in which a person is integrated in all levels of being—that is, in body, mind and spirit. One might ask several questions: What is holistic health and what does it entail? What is involved scientifically in the holistic view of health care? Is it just a curious or exotic term, or are there real values in this approach to health care? My own concerns involve both curiosity and caution. I am curious as to its accurately applied meaning and cautious as to whether all its elements are scientifically sound, as well as how they will fit into our traditional pattern of health care. Further, I am concerned about the ethics of recommending therapies for which there is no scientifically proved effectiveness as yet.

It has been suggested that many modalities of treatment may be used in holistic healing. To achieve this, it will be necessary to tap the resources of our most learned scholars, sophisticated researchers and expert clinicians and practitioners to teach each person to assume responsibility for himself and to heal himself through modification of unhealthy attitudes, values or life-style.

If we physicians admit there should be alternative approaches to the traditional management of disease, of life, and of death and dying, then might this be the place for holistic care? Certainly, there is need for modifications in life-style in dealing with stress and tension; so too, new perspectives may be needed in the treatment of organic disease. Therefore, we need to learn and evaluate life-long modification skills that have been derived from ancient cultural traditions, and how we might integrate them with new technologic discoveries.

The responsibilities of a doctor to his patient were clearly outlined by Hippocrates more than 2,300 years ago when he emphasized that physicians must consider the whole man to diagnose and treat properly health care problems. He pointed out that the well-being of a person is influenced by social and environmental as well as physiological changes, and that the art and science of medicine include consideration of all these factors.

Refer to: Todd MC: Interface: Holistic health and traditional medicine, *In* Orthodox medicine, humanistic medicine and holistic health care—A forum. West J Med 131: 464-465, Dec 1979

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The original Hippocratic oath bids each physician to swear by "Apollo the Physician, by Aesculapius, and Hygieia and Panacea. . . ." Hygieia, of course, is synonymous with the prevention of disease . . . and calls on the physician to be concerned with preventive as well as therapeutic medicine.

This thesis was reinforced in the Hippocratic doctrines which stated "The well-being of man is influenced by all environmental factors . . . the quality of air, water and food, the winds and topography of the land . . . and the general living habits." Therefore, understanding the effects of environmental and social forces on human beings is important if the physician is to practice the art, as well as the science of medicine.

But Hippocrates lived in much simpler times . . . long before the revolution in science and technology which has transformed our lives, bringing with it *problems* as well as progress.

Menninger[2] implies in his writing that there is a striking inability on the part of doctors and psychiatrists to practice a form of holistic medicine that integrates knowledge of the body, mind and environment. Resistance by the medical profession to these new approaches may be due to conceptual polarities in medicine, such as body-mind dualism or the separation of health from illness.

Dr. Daniel Feldman,[3] of the University of California, Irvine, states "The holistic view of illness postulates that it is a composite phenomenon, contributed to and shaped by a number of influences, which may or may not bear a direct causal relationship to each other." He maintains that management of illness requires an understanding of as many of these influences as possible. Such an attitude is important, particularly to patients with chronic disabling disease, because their illnesses involve not only organic medical problems, but social, economic, environmental and behavioral problems, as well. Chronic disabling conditions should be examined within the context of a total human environment and involvement. For example, holistic medicine should serve as an interface between those patients who have psychiatric and behavioral problems and those methods of treatment needed to control or cure these conditions.

Our contemporary system of medical care in the United States is one of detection and cure; it is not geared toward prevention of disease or promotion for good health. It has been said that the goal of holistic health is promotion of vigorous well-being both as an individual and societal commitment. Therefore, it is up to each of us to make changes in our own life-styles and environment that will bring about good health.

But society should be aware of the charlatans who advertise themselves as holistic healers, yet who are without any special qualifications. We can see a full complement of colorful characters . . . Chinese herbalists, psychiatric healers, Indian shamans and some medical doctors all vying for "a piece of the action," which leads one to ask, "Is it really good, or is it not?"

Medical care alone cannot bring about substantial improvement in the health of all people; it may need the accompaniment of better behavioral, social and environmental concepts. Dr. Richard Chilgren, Associate Professor of Pediatrics, University of Minnesota (personal communication, February 1978) has said

> The term holistic health may in some ways be a catch-all of alternative approaches to health care. But more than that, the phrase implies—if not a specific direction—at least a trend already evident in many places, that perhaps may be reflected in the integration of mind, body and spirit, or by a redefinition of health to include a sense of consciousness-raising or growth.
>
> On the other hand, in perhaps a more ethical sense, holistic health addresses the human energy crisis; the energy-sapping life-style problems which are less amenable to the technologic approach to medicine. It redirects us to the importance of exploring our inner space, or consciousness, through emphasis on health education and responsibility for self.

So it seems proper and timely that the medical profession and its related organizations become informed about and involved in some of the acceptable alternative programs to health care as we work to improve the traditional approach to care.

REFERENCES

1. National Symposium, September 15-16, 1977, Granger Westberg Wholistic Health Center, Inc., Hinsdale, Ill.
2. Menninger RW: Psychiatry 1976: Time for a holistic medicine (Editorial). Ann Int Med 84:603-604, May 1976
3. Feldman DJ: Chronic disabling illness: A holistic view. J of Chronic Dis 27:287-291, Aug 1974

Holism and Reductionism as Perspectives in Medicine and Patient Care

RICK J. CARLSON, JD

MOST OF WHAT is being written and said about holistic health care further confounds an already confused understanding of the concept of *holism*. In an attempt to clarify rather than confound, I will discuss some more important problems involved in integrating holistic health with the practice of modern medicine in the United States. But first, a little history is in order.

A Brief History of Ideas

In the early 1800's, memories of the plagues were not too far in the past. Population size was steadily increasing, and more important, food supplies were increasing as well. Infectious diseases were the major killers, but the rates of these diseases had already begun a slow decline which was to continue into this century. The practice of medicine at that time was more systematic than many of its shamanistic roots, but it still lacked a method of inquiry and a method of linking cause and effect. Traditional beliefs were strong and were primarily Judeo-Christian in nature. Hence, the *responsibility* for health was placed largely outside of individual persons; it rested in the relationship between each person and God, and was more dependent on God's beneficence than on human agency.

In the decades leading to this century two critical developments took place. First, a scientific method became available which served as a means of transforming the idiosyncrasies of medical practice, and the ungrounded assumptions on which they rested, into a more systematic form. Second, public health programs were initiated because relationships had been perceived, finally, between certain environmental factors, such as water quality, and levels of health of persons exposed to them. These two developments, based on a common epistemology—cause and effect relationships, were major steps toward the medicine of today.

At the turn of this century and into the early 1900's our society had some fundamental options before it. What evidence there is identifying those factors associated with improvements in human health before the beginnings of the century suggest that the principal gains were achieved through non-therapeutic methods, principally public health measures, and improvements in the quality and amounts of food. Yet, therapeutic medicine was gaining ascendancy. At the same time, and perhaps more important, medicine was gaining in political and economic strength as the number of its practitioners increased. The Flexner report, issued in 1910, led to near monopolistic control by allopathic medicine over the institutions of health.

In my view, the choice to develop a system to deliver medical care through nearly exclusive allocation of resources for that purpose, was made more for political, social and economic reasons than for therapeutic ones. A careful reading of the historical record at the turn of the century would have suggested continuing and even amplifying programs designed both to improve the quality of the environment and to further strengthen human hosts. Nevertheless, and in many respects contrary to choices made by other societies faced with similar problems, we in the United States chose to create and progressively claborate a medical care delivery system as a means of improving our health.

The results of that choice have been significant.

Refer to: Carlson RJ: Holism and reductionism as perspectives in medicine and patient care, *In* Orthodox medicine, humanistic medicine and holistic health care—A forum. West J Med 131:466-470, Dec 1979

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We have gained impressive information about human biology, as well as about illness and the means of curing and treating many of these diseases. And, there is probably much still to be learned, making further investments in biomedical research necessary to fully understand disease in humans. Yet, we may now be poised for a fundamental change in perspective—a change that may restore the influence of social, environmental and behavioral factors on public policy decisions regarding health care.

This brings us to the present and to the problem facing us of widespread disillusionment with doctors and hospitals. Hopes, even fantasies, about new approaches to medical care abound, many of them springing from the premise of holism. And many serious, scientific and policy questions are being asked about how to best integrate the old with the new, if at all.

The Question of Integration: Policy Issues

There are many significant scientific and technical issues regarding the variety of new approaches to health care, but this paper addresses only those which are clearly policy issues, although the distinction is often hard to make. In my view, policy responds more to pressure, opinion and belief than to evidence. Indeed, evidence is often a by-product of a position or opinion. The scientific debate will continue, and should. But given that, what are the policy issues?

The Difference Between Concept and Technique

The term holistic, first coined by Jan Smuts in 1926, has come to be applied to almost every aspect of human behavior. The original use of the word by Smuts was epistemological; it was a way of characterizing phenomena in a profoundly different manner than in the prevailing *reductionist* perspective. To Smuts and others, the reductionist perspective resulted in an unrelenting analysis of the parts of systems without consideration of how those parts interacted in larger systems, and without consideration, or even acknowledgment, of phenomena which represented more than the sum of any set of parts. Thus, holistic thinking in its original and fullest sense is an antidote to the reductionist epistemology which underlies modern scientific thought.

In recent years holistic has been applied frequently to aspects of health care; perhaps more frequently than in any other sector. It is hardly an assault on human sensibility to examine the chemical constituents of a substance one at a time. But to many thinking and feeling people it is not only limiting but impoverishing to assume that health is nothing more than the composite of well-oiled body parts. In this sense, the application of the term holism to medicine is more than timely; it is profound. Unfortunately, the term is often glibly used or made trival.

The term holistic has been applied to health and medicine, essentially, in three ways. The first and least important way has been to describe a variety of *new* therapeutic modalities, such as biofeedback practices, acupuncture or various methods of body work like the Feldenkrais technique and rolfing. But, while practitioners of these healing arts may be holistic in their orientation—that is, in how they perceive and interact with their clients—the modalities themselves are no more inherently holistic than coronary artery bypass surgical procedures. The power of holism lies in its *perspective,* which is more an epistemological concept than a practical one. Holistic health, in many respects, has become a banner under which parade practitioners of various healing arts, some efficacious and others not, who seek the legitimation of their practices within holism, having been denied that legitimation elsewhere.

A second application of the term has been to describe a political movement. In California and in other parts of this country, the holistic health movement is a constituency with political as well as therapeutic objectives. Traditional medicine gained its ascendancy through political stratagems, not through the inarguable superiority of its therapeutic impact. Hence, to practitioners who are outcasts of traditional medicine, and to consumers whose dissatisfaction with traditional medicine is acute, political agitation is expedient. In California, where holistic practitioners are legion, and where the number of consumers interested in holistic practices is large and growing, those involved with holistic health form a constituency with real political leverage. There is nothing wrong with arguing the holistic case as a means of allowing fresh thinking into the practice of medicine. But this is not necessarily its most profound application.

Again, the power of holistic thinking lies in its ability to awaken our perceptions of who we are as human beings. Reductionist thinking in any

area results in compartmentalizing human experience into those aspects or parts which are amenable to detailed analysis or intervention (or both). This is one of the root premises underlying prevailing medical practice. And, although it has its uses, it is a profoundly limited view of human beings. Holistic thinking, as an epistemological notion, requires that human beings be perceived as whole persons made up of physiological, emotional, intellectual and spiritual dimensions that dynamically interact, and that any approach to improving the health of human beings, either individually or in groups, requires placing them in a larger and richer context than does traditional medicine.

The shift towards holism is irreversible. Not because it is being forced on medicine, but because the shift is part of a much larger change in perspective regarding humans and their conceptions of themselves. Its application to medicine, then, is one aspect of a broader paradigm. The perspectives of holism are influencing human thinking and acting at many levels. And this is why the concept has so much more power and potential effectiveness than can be appreciated by attending a conference on holistic health in California, where the message is that carrot juice, massage and holistic running clinics represent the state of the art. This does not mean that all holistic practices can be integrated easily into existing approaches to treatment. But it does mean that the future practices of medicine will be influenced unmistakably by the holistic perspective.

The Scope of Medical Practice: Can Doctors Become Nutritionists, Too?

In recent years the push towards a holistic perspective on health has presented even sympathetic physicians with a dilemma. Many thoughtful physicians recognize that there are many facets of health care for which their training never prepared them. Moreover, most acknowledge the critical importance of environmental and behavioral factors, nearly all of which lie beyond the scope of modern medical training and practice. Under these circumstances, there are some who argue that, as a matter of policy, physicians and other health professionals should be trained to better understand the roles that environmental and behavioral determinants play in health and illness.

On the other hand, there are those who argue that the burden of medical education is already so great that to broaden it would place intolerable pressures on students. It is true that physicians and other health professionals are rarely trained to understand the importance of a wide range of environmental and behavioral factors associated with human health, but it does not follow that education of health professionals must be broadened to embrace those concerns. In fact, the opposite option is to continue existing training programs for health professionals and, in particular, to intensify the physician's training as a technician for those who are already ill. To continue this argument, the technical skill and expertise of physicians are required for those health problems which many of us encounter when it is too late to take preventive measures. The corollary is that if other determinants of health require attention, then other health professionals should be specially trained to deal with them.

Recently, in California, under a directive of Governor Brown, medical schools receiving state funds were required to propose budgets which shaved the costs of medical education. The schools responded by proposing a curriculum that diminished information to students about nutrition. This decision caused much anger in those who felt that nutritional issues would be ill served. Yet, the response of the medical schools, perhaps for the wrong reasons, was possibly very rational. Nutrition, to take just one example, is a complex and controversial subject. Hence, the decision of medical schools to curb nutritional information further for physicians in training, was a response, at least in part, to the need to simplify and streamline medical education so as not to bewilder further the already confused student. The reasons the medical schools gave may have been the wrong ones, but the result is consistent with an emerging view that the way to better health is to have more highly trained physicians-technicians, *as well as* other trained health professionals to handle those issues beyond the scope of conventional medical education.

A movement in this direction, of course, may fail to resolve several other critical policy issues. While many physicians and organized medicine, itself, are sympathetic with both the need to train other health professionals and to develop public programs to influence the levels of health of populations, they remain loathe to part with any of the

money they receive for medical practice. This position is hard to reconcile because the evidence is growing that environmental and behavioral interventions are more likely to improve our health than continued resource allocations to medical care. Hence, the issue of resource allocation is far from resolved, even assuming that the question of educational scope can be settled.

There is also the question of *stature*. As long as physicians insist on remaining in control, as they have done historically, an education for health professionals that emphasizes behavioral and environmental considerations is not likely to attract the calibre of students that medical education characteristically attracts (there is another set of arguments which describes the *narrowness* of the typical medical student). Unless health professionals, who are trained in environmental and behavioral areas, are given equal stature in the overall health care system, their training programs will continue to be impoverished as future decisions about resource allocation are made. This is another issue that must be faced.

The Epistemology of Practice: Belief and Result

Susan Sontag, in her book *Illness as Metaphor,* attacks holism for making the reality of sickness and disease trivial by treating it as a metaphor. She vigorously disagrees with the holistic concept of responsibility, and at its further reaches, the idea that people *choose* their sickness, often even the form. To Sontag and to many in traditional practice, disease or sickness is a phenomenon that simply happens to a person largely beyond his or her responsibility or fault. Sontag is angry about the holistic interpretation because she, having experienced the ravages of cancer, directly confronted the brute reality of her sickness.

This holistic view is radically different than the underlying premise of conventional practice that disease is indiscriminate in its striking, save that a person's constitution may predispose him to a certain condition because of inherent weaknesses or because he is *run-down.* This fundamental difference in perspective is very crucial to the question of integration.

There is some persuasive evidence about the role of belief. In a recent study, for example, a substantial number of persons' death dates were compared with their birth dates. It was found (with a statistical number of sufficient size) that a disproportionate number of elderly people die within three months following their birthdays, as opposed to a smaller number of people who die within three months before their birthdays. In addition, recent research on biofeedback practice, shows that the sophistication of the equipment notwithstanding, the single most important factor in patient outcome is often who is in the room with the patient; how does the technician, with a machine along for the ride, interact with the patient? That seems to be what makes the difference. Finally, the work of Carl and Stephanie Simonton, reported in *Getting Well Again,* shows the importance of motivation and patient participation.

The point is that if one approaches the problem, whether as a practitioner or not, with the assumption that the patient has somehow *chosen* to be ill, the therapeutic approach recommended will necessarily be very different than if one approaches that same person, assuming that the illness is beyond his responsibility. This difference makes the question of integration problematic.

Money and Truth: The Origins of Modern Medicine

I recently gave a talk to a group of physicians at a California Medical Association meeting. I began by asking them to imagine themselves in the same room at the turn of the century. I told them that if we had all been here at that time, about half of us would have been homeopaths. The practice of medicine before the 1900's was mixed, with a variety of medical theories competing, particularly homeopathy and allopathy. Then, in the years between 1900 and about 1920, homeopathy was driven underground. One way to interpret this was that the superior therapeutic efficacy of allopathic practice, the theory on which modern medicine is based, simply won the day. Yet in Coulter's book *The Divided Legacy* and in other places, history looks different. It looks instead as if the virtual disappearance of homeopathy had much to do with the economic and political power of allopathic practitioners.

This is a controversial proposition, but even if it is only partially true, it suggests, again, that the question of integration is not likely to be resolved on the basis of therapeutic weaponry, but rather on politics and economics. Under these circumstances, holistic practitioners, the power of the concept of holism notwithstanding, are at a decided disadvantage. If the existing system chooses

to suppress holistic practice, if history is any guide, it may well succeed, regardless of the belief by many practitioners and patients that holistic practices should supplant conventional medical practice. This does not mean that some type and limited amount of integration will not occur. In fact, it does not preclude a drift in philosophical orientation of the present system towards holism. But it does suggest that any expectation that holistic practice will overcome allopathic practice is unrealistic.

Conclusions

What is important is the concept, not the technique. Techniques always follow ideas. The holistic idea is what is important in the future. Institutions are not based on thin air; they are created as a result of ideas that have gained the allegiance of a sufficient number of people to make them real. The holistic idea is one whose time has come and, while the institutional manifestation of holism is not yet clear, I think it will become evident during the next few years. However, it is unrealistic to expect a radical transformation of medical practice. The premises of traditional practice are strong and will certainly compete with the holistic perspective. Moreover, the political, the economic and, indeed, the social and cultural strengths of the current system outstrip those of any competing alternate system. This does not weaken the idea of holism, but it means that it must find its way gradually into institutional practice. In fact, and this may be my most important point, if it were possible to integrate holistic practices completely with existing practice, the result would probably be the impoverishment of holistic practices rather than the enrichment of conventional medicine. The power of the holistic approach to health and healing is that both the therapist and the client (or patient) approach the problem with the same perspective. This means that the provider of services, or the therapist, attempts to see the person as a whole, while guiding him through a healing process that makes sense for this person. And assuming that this person is unwilling to accept a one-treatment approach to a complex problem, he will fully participate in the process. It is very difficult to transform that kind of experience into reimbursable units of services in the same manner in which an injection, a surgical procedure or a drug can be prescribed and in turn paid for, piece by piece. There are some *practices* associated with the holistic movement, such as biofeedback and certain diagnostic techniques, that can successfully and realistically be integrated into conventional practice. But most of what is rich in the holistic orientation must necessarily remain outside a fee-for-service medical care system. And this is so because to integrate the perspective, as it translates into practice, is to erode the practice, and in turn, vitiate the perspective.

In the final analysis, the holistic perspective is here to stay. It is hoped that some of the practices can be made more widely available to persons through the existing system of medical care services. But, much of what is important and, in the long run, powerful, about holism, must remain outside of any organized medical care system. It must, for that reason, have something to do with the way life itself is lived.

What Is Health For?—Human Priorities in Health Care

JAMES VARGIU, MA, and NAOMI REMEN, MD

THE AMOUNT OF MONEY spent each year in the United States on products that are believed to enhance and promote health, and the amount of time spent by people in jogging, dieting, exercising and otherwise strengthening their bodies, suggest that physical health is something that most people see as extremely valuable. Useful as many of these activities are in maintaining health and preventing disease, the quantity of energy expended in this drive for health leads us to pause and wonder. Is health a quality so intrinsically valuable that it should be sought and possessed for its own sake? Or is health, like money, valuable only because it can be used for another purpose? Is being physically healthy an end or only a means? Why be healthy?

Such questions offer an interesting opportunity for us as physicians to bring into clearer focus the principles which guide our professional decisions and the priorities which govern our therapeutic actions. Consider the following case history.

Reginald Mitchell was an Englishman who died in 1937. At the time of his death, he was world famous as the designer of the airplanes that brought victory to England year after year in the international Schneider Cup air races. In 1933 he was found to have cancer and he underwent extensive surgical procedures from which he never fully recovered. A year later, during a trip to Germany, he became concerned about what he saw happening in that country. He spoke to people in the streets, met personally with Hermann Goering and, because of his expertise in the field, was shown the German air force. He was tremendously impressed with the advances Germany had made in the design of its planes. With a sinking heart, he realized that the technology evident in these German aircraft far exceeded anything comparable in England. He returned home and reported to Whitehall that he felt the safety of his country was in possible jeopardy because of Germany's advanced air capacity. He was able to convince the government of the danger and received clearance to design a plane that would allow England a chance of defense in the event of war with Nazi Germany.

Soon after he started to work, relations between the two countries began to deteriorate. Mitchell worked 18 to 20 hours a day, seven days a week. Under this stress, his fragile health faltered and he consulted several physicians, all of whom advised that he must stop his work. He ignored their advice and pushed on, while his health continued to fail. Finally, he was told that he simply could not continue doing what he was doing; at his present pace, he would be dead within the year. His response was "I think a year is all that I need. Can you keep me going?"

After much thought, his physician decided to give Mitchell the support he asked for, and barely 20 months after his return from Germany, the final designs were completed and emergency production of the plane had begun. On March 5, 1936, he watched its maiden flight from a wheelchair. The Spitfire performed exactly as he had planned and became the critical factor in England's successful defense against the Luftwaffe. Six months later, Mitchell died. He was 42 years old.

Mitchell was a man who *spent* his health, who used it to do something that was more valuable to him than health itself. For him health was a personal resource which enabled him to express his priorities and sense of purpose. Mitchell and persons like him inspire us to reexamine the context in which health occurs, the subjective realm of purpose, aspiration, values and meaning. In some ways, Mitchell's life was healthier than that of persons who are physically healthy but who find life meaningless. He was a man who chose

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to live by his values and, in doing so, presented his physician with a difficult choice. In point of fact, his physician chose to help Mitchell live in this way, to *keep him going* so that he could act in keeping with something that gave him not only personal satisfaction but the opportunity to meet a need greater than his own.

Technically, Mitchell was a noncompliant patient, and in the same class as a man with emphysema who smokes or a woman with pancreatitis who drinks. Yet, when he ignored his doctor's advice, his doctor responded not by refusing to condone such self-destructive behavior, but by using his medical knowledge to support his patient toward his goal. How many of us would be open to consider the appropriateness of responding in this way? It is difficult to reconcile this action with the traditional dictum that a physician's primary responsibility is to preserve physical health. When can this more orthodox approach justifiably be tempered by a consideration of a patient's individual sense of purpose and his wish to use his health in accordance with it?

Patients like Mitchell may not be so rare. Many people value something that enhances the meaning and quality of their lives more than they value health itself. Mitchell's case is dramatic in that he gave his life as well, but less extreme cases frequently pass unnoticed in the daily practice of medicine. If we examine our own health care experiences we see that many of our patients choose to get a little less sleep, skip a meal or return to work before they are completely well to do something that is important to themselves and to others. Physicians use their own health in this way all the time.

This seeming abuse of health may be common enough to raise some difficult issues for us in our professional role. What is the responsibility we have to people who use their health in this way? Is our traditional frame of reference broad enough to make such decisions, or does it need to be expanded?

A sense of purpose is a distinctively human quality; in supporting it we support what is most essentially human in our patients.[1] Yet the spectrum of human purpose is broad; some people place the highest priority on their own personal comfort or pleasure, others on the welfare of those they love, still others on principles or causes which are of benefit to society in general.

The diversity of this range presents a difficulty in determining which of these many goals and purposes warrant our professional support. If we support someone like Mitchell in his goals are we also obligated to support a cardiac patient whose choice of an expensive life-style demands that he work a 70-hour week, or a professional athlete who demands periodic methandrostenolone (Dianabol) in order to lift weights more effectively?

The choice of individual purpose and direction is unquestionably the domain of each person. No one can tell another what this purpose is or should be. Yet in supporting this personal freedom of choice, are we also to support the choices themselves, indiscriminately?

The practical approach to such questions seems to require a perspective greater than that found within medicine itself. The individual sense of the meaning and purpose of human life which we bring to our medical practice deeply affects the way in which we respond to these issues. To see the prolonging of life as a goal sufficient in itself will probably lead us to see health as an end in itself. To see life in a larger frame of reference, as including a person's individual direction and purpose as well as a direction and purpose beyond this person, will enable us to see health as a means that can be used appropriately to reach these larger goals. The issues involved, therefore, encourage not only a reexamination of our responsibilities and priorities as physicians, but also point to the relevancy of our own world view to our practice.

It appears that the perspective in which Mitchell and his doctor saw health is worthy of our consideration, as we attempt to act in ways that acknowledge the full humanity of our patients. Is human health indeed only an end in itself, or is it actually a means toward a greater goal? Should we, as physicians, consider the growing human need for meaning and purpose[2-4] in the same careful and responsible way in which we presently address the needs of the body? Is the current drive towards physical health as the ultimate goal and defense against death at any cost really the best and most satisfying way to live?

REFERENCES

1. Jonsen AR: Purposefulness in human life. West J Med 125: 5-7, Jul 1976

2. Maslow AH: The Farther Reaches of Human Nature. New York City, Viking Press, 1971

3. Frankl V: Man's Search for Meaning. New York, Washington Square Press, 1963

4. Vargiu R, Firman J: Dimensions of Growth. Synthesis; The Realization of the Self 3:59-121, 1977

Holistic Health and Medicine: A Challenge

LEONARD J. DUHL, MD

A TREMENDOUS AMOUNT of discussion is taking place about holistic health and, as one listens carefully to the variety of dialogues, one hears many messages. At one end of the spectrum is the view that modern medicine is completely inadequate and must be replaced by another system; at the other end is the view that a variety of techniques exist that could supplement modern medicine. Within this range there are issues more directly related to the problems of healing the sick that must be faced every day by those in the medical community.

Some physicians complain about the complexity and confusion surrounding these problems. Others speak of Medicine's fragmentation and inability to deal with issues in a comprehensive and thorough manner because of lack of time and money. I believe that we are being faced with problems that extend far beyond the fields of medicine and health care. Many of these have been laid on the doorstep of Medicine as if, by dealing with the medical-health problems, all else will fall into place.

In some ways, hospitals and the medical establishment have replaced cathedrals and the Church as the focal points of attention in a society that at one time hoped and dreamed that the Church could provide answers to questions regarding the totality of existence. The medieval church, as strong as it was, proved unable to do this and we as physicians are—or should be—too wise to claim that we are capable of dealing with such broad issues.

The words *health, medicine, health care* and *medical care* are used much too loosely. Medicine is related to the ill; health to a sense of well-being and not just the absence of illness. And what is called health includes a concern with the good life and the totality of our existence. Yet if we have failed to come to grips with that totality of existence, it is not because of a lack of medical care but because we have neither reached an adequate comprehension of nor developed the social mechanisms needed to deal with the vast complexity and interrelatedness of the *organism called Earth.* Furthermore, as physicians or others concerned with human behavior, we must be humble in realizing that there is much we still do not know about the *organism* known as a *human being.*

Nevertheless, physicians have been faced with the dilemma of how to deal with human beings in their pain and illness. And because the problems surrounding both the human organism and the organism Earth press upon us with such intensity we are forced to look continuously at alternative methods of perception and intervention.

As in the field of medicine, those intervening in our society have tried hard through scientific means to understand fully both the human and social organisms and how they work. Many have tried techniques which have been called rational and scientific to tease out the complexities. Through models, Cartesian in nature, attempts have been made to control or intervene in the behavior of human beings to make them healthy. The same attempts are being made to understand and control our earth.

We are endlessly faced with *not knowing.* We have searched for answers in biological, psychological and sociological areas. Though at times we have found a separation between *psycho* and *soma,* increasingly we are encountering difficulty with this division. We have become more aware that in human beings, we cannot separate the psyche and the soma, or the social context in which the two exist.

I believe that behind most holistic dialogues is an awareness that we cannot separate internal from external environments. We cannot disregard problems that we have called *internal homeostasis* from questions of the homeostatic balance of the

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external world. Thus, health becomes a synthesis of the internal and external environments, and holistic means the integration of all parts of the whole. Does this mean that physicians have to deal with the problem of the holistic totality and interrelatedness of the organisms, Earth and human being? Again, my answer is that this is neither our wish, nor our capability. And yet we must place our actions as physicians within the context of holism. What has resulted is physicians becoming members of more complex teams of specialists and integrators who assist in the process of trying to make human beings whole within a larger social context—earth.

The so-called holistic health explosion has forced us to face the fact that there may be alternative ways to view the human organism. Energy and Chi models, previously foreign to American medicine, are being incorporated into our work. In addition, there are persons who are endeavoring to show us that there is more to medicine than a rational, scientific approach, both in our ability to understand medical problems and in our intervention to solve them. These persons are forcing us to look at Eastern philosophies—Tao and Buddhism, for example—as well as extensions of scientific medicine such as biofeedback, all of which contribute alternate ways of understanding that may prove helpful. If we respond by looking further, we show respect for other cultures and beliefs that have worked well in helping some people, and an openness to the possibility that there are other ways to cope with problems and issues that primarily have been called medical. Indeed, as we become more open, we find additional scientific, rational answers to questions and techniques we heretofore considered irrational or, at best, nonrational.

We need to ask whether modern medicine, magnificent as it is, can cope with all the issues concerning either human beings or the contextual Earth. If we cannot cope, we need to develop new relationships with persons who are concerned with these issues and who may help by offering different conceptual models.[1]

This is a difficult path, for we may not know how best to synthesize such a diversity of viewpoints, concepts and issues. Though we have toyed with the integration of religion and medicine, concepts of the soul and of physiologic medicine have been difficult to integrate with science. The path is frightening because it means giving up or letting go of the notion that we—and we alone—have the truth. There may be other truths.

If health is primarily a concern with human growth and development, and with a variety of forms offered by genetic and other heritages, we have a task that is more simple. In this process all aspects of society are involved in what I call *societal education*. In this context, physicians contribute but do not have prime responsibility. It involves all of the organism Earth.

As the normal developmental process of the human organism is unbalanced by pressure and crisis in moments of tension, the possibility of *dis-ease* occurs.[2] Dis-ease comes in many forms, one being medical illness. It is here that physicians play a primary role; and it is here that we must work closely with others to show that there is a possibility of jointly contributing to the treatment of illness.[3] Our work does not end here, for although some people remain chronically ill (and must receive appropriate assistance, too), others must be helped in the healing process.[4] It is here that we as physicians must again engage in joint relationships with others, with a focus on healing that may involve social networks, a sense of community and much more.[5] All of this is holistic medicine.

We as physicians own a monopoly only in our particular expertise, and unless we work with others with different views, we will never have holistic medicine for human beings nor holistic health for the organism Earth.

REFERENCES

1. Knowles JH: The responsibility of the individual. Daedalus, Winter 1977, pp 57-80
2. Williamson GS, Pearse IH: Science, Synthesis, and Sanity. London, Collins, 1965
3. Health of the Individual, of the Family, of Society. Pioneer Health Center, Rotherfied, Sussex, Engand, 1971
4. Pearse IH, Crocker LH: The Peckham Experiment: A Study of the Living Structure of Society. London, George Allen & Unwin, Ltd., 1947
5. Duhl LJ, Den Boer J: Making Whole: Health for a New Epoch. New York, Pergamon Press, Inc. 1980 (In press)

Holistic Health: A Valuable Approach to Medical Care

MARC LAPPÉ, PhD

CONFUSION OVER THE ORIGINS, validity and usefulness of holistic health abounds. Medical practitioners, long used to offsetting the irrational approaches of health fads, neuropathic treatments and home cancer remedies are understandably cautious about embracing what appears to be the newest fad of the counterculture. Such a response would be unfortunate because the approach of holistic health itself and many of its specific therapeutic regimens are rooted in traditional medicine. More to the point, I am convinced that the philosophy of holistic health carries a very important message to practitioners facing contemporary medical problems ranging from antibiotic resistance to refractory psoriasis: namely, that new directions in medicine and health care are likely to be holistic because the problems they must address demand it.[1]

The deepest roots of the holistic health movement can be traced to Eastern cultures, most notably the Chinese.[2] Common to both historic and current approaches is the belief that most disease processes involve multiple organ systems, and that health and treatment of illness generally depend on viewing a person in relation to his surroundings. This means admitting that most health problems entail a multidisciplinary approach that acknowledges the force of external factors—including social, political, cultural and physical environments—on health and its maintenance. In the holistic view, disease processes should be understood in a broader context than linear causation; that is, as resulting from the interactions of multiple factors.

Lest this seem too sweeping and vague, let me offer a few concrete examples. Major arthritic conditions, particularly those associated with relatively aggressive autoimmune reactions, form one of the most common categories of disorders requiring multiple office visits. Long thought to be precipitated by a bacterial infection, family history or just plain old age, diseases like rheumatoid arthritis were (and still are) treated symptomatically, with little or no attention to possible underlying causes. Advances in immunochemistry and genetics in recent years have brought about a recognition that a multiplicity of factors apparently interact to initiate the disease process, no one of which alone being the causative agent.

These advances have also provided evidence of the immense storehouse of genetic variation among persons. Holistic medicine has long stressed what orthodox practitioners have only recently come to recognize as a fundamental theorem of modern medical practice: human beings vary significantly in their basic biochemical makeup. This variability now rests on a solid genetic base: Each person's biochemical makeup is qualitatively different from another's (with the exception of identical twins) because of the existence of genetic heterogeneity. About 30 percent of all the genes in the human species come in different allelic forms. This means that it is possible to be heterozygous at a minimum of 15 percent of the 70,000 to 100,000 genetic loci that we carry.[3] Moreover, recombination and gametic choice vastly increase the chances for variation made possible by the multiple forms (polymorphisms) of so many of our genes.

The relevance of this reservoir of genetic variability lies in the fact that each person individually adapts or reacts to environmental stress and circumstances; and that what constitutes health will vary according to these idiosyncrasies.

The HLA locus is typical of these polymorphisms. It is a cluster of at least four related genetic loci on the sixth chromosome. An allele at one of these loci, known as HLA-B27, is strongly associated with the appearance of ankylosing spondylitis.[4] More than 95 percent of all young males in whom this often debilitating syndrome develops have the antigen. Apparently, the

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antigen alone is insufficient for precipitating the disease, because less than 2 percent of all B27-positive persons develop the syndrome. A second tier of evidence implicates several bacterial species, most notably Klebsiella, Brucella and Yersinia, as having a precipitating role in this illness because it often follows closely on the heels of a reported infectious episode. A third factor involved in the genesis of ankylosing spondylitis appears to be stress. A history of back strain, long hours of sitting and direct physical injury to the back have been associated with the development of the disease. Psychogenic stress, with or without an overlay of symptoms of psoriasis, is yet a fourth factor. And finally, there are the patients with *uncomplicated* ankylosing spondylitis, for whom none of the above conditions apply. Clearly, this is a multifactorial and complex disease entity.

The association of at least 40 more disease processes with the HLA system clearly indicates that many diseases previously thought to be caused solely by outside agents actually result from a combination of internal *and* external factors.[5] Holistic approaches acknowledge this complex causation as one of their starting points. While such a belief appears almost too simple, it is one of the first points any second-year medical student hears in a pathology lecture. It is the *emphasis* on seeking multiple causes—and treatments—of pathological processes that is new. Holistic medicine stresses the interdependence of organ systems in disease processes, much the way endocrinology research first linked the major glandular systems. And although many of these associations lack an empirical base at present, others, such as the interrelationship in the adrenal, lymphatic and neurohumoral axis, appear well-grounded in biological fact. A growing acceptance of the role of the immune system in the production of tumors implicates additional organ systems in the pathogenesis of cancer. Like it or not, the fact that stress and psychogenic factors can influence immune reactivity provides a rational hypothesis for the mutual interactions of mind and body, a claim which holistic practitioners have made for years.

A second example of how holistic approaches work may be seen in the incompletely understood problem of toxicity associated with the use of dioxin-contaminated phenoxyherbicides. The presumption that chlorinated small-molecule hydrocarbons would be relatively innocuous to humans was based on the faulty premise that human metabolic systems would be unaffected by novel molecules, except for nonspecific detoxification reactions generated by the microsomal system of the liver. Consequently, the dioxin contaminant went unrecognized as a major health hazard.

We are learning quickly that dioxin contamination has reverberations throughout the ecosystem, and that its effects on humans may be more subtle and long-lasting than the simple toxic reaction known as chloracne as first reported. Differential susceptibility and dependence on serum levels of iron for toxicity,[6] extraordinarily persistent effects of enzyme disturbances,[7] and possible involvement in the development of birth defects suggest that the network of potentially harmful effects of dioxins should receive the broadest investigation possible.[6] One of many interactions which could well be studied using a holistic approach is the production of elevated triglycerides by halogenated aromatics like dioxin (2,3,7,8-tetrachlorodibenzoparadioxin) which may be particularly harmful in those workers who have raised levels of lipids due to the relatively common genetic defect responsible for type II hyperbetalipoproteinemia. Because these and other enzymatic changes go on for years, dietary factors and life-style adjustments should be reviewed by conscientious doctors who wish to avoid the composite problems of heart disease and atherosclerosis in dioxin-exposed patients.

Specific Areas of Application

At their best, holistic approaches complement and reinforce several major areas of medical practice.[8] Practitioners may recognize forms of treatment and ideas that they have already incorporated into practice which are embodied in the holistic philosophy. Knowing that one's ideas coincide with a holistic approach does not necessarily validate them, but it does provide a basis for further broadening one's perspective towards new or alternative approaches to practicing medicine.

Humanistic Medicine

The concept that health care should fully consider human needs while embracing humane attitudes, ethics and behavior has recently regained popularity. Many practitioners, in fact, see such an approach as a necessary standard for our medical system. Minimizing the use of therapeutic interventions and choosing the least restrictive or damaging options when they are needed, as well as reducing patients' reliance on drugs have re-

cently been reemphasized. Not coincidentally, these practices are integral to the holistic movement.

Holistic Medicine

The term holistic medicine has been misused to cover a spectrum of new or unconventional approaches to medical practice, from embracing orthomolecular medicine and psychiatry to treating asthma and allergy. Many of these approaches, such as orthomolecular medicine, are relatively untested; others, such as allergen treatments by sequential elimination of offending substances, have received widespread acceptance. For example, the fact that migraine headaches often respond to the elimination of major foodstuffs with allergenic properties (beef, peas, wheat, and so on) has been reported recently in a prominent medical journal as a major advance.

Adoption of optimal health practices, an essential component of holistic medicine, has received increasing recognition within the medical community as part of an overall approach to teach persons to take control of their own health-related behavior. Holistic medicine also bridges the barrier which has traditionally divided Western medicine into two separate domains—one treating diseases of the mind and the other diseases of the body. The most radical extension of this approach is to identify all health events as part of a continuum of systems extending from the molecular to the ecological.[9]

Alternative Health Care

Holistic health actively encourages the proliferation of systems and approaches to health care which use nontraditional methods to treat disease as alternatives to orthodox regimens. Therefore, holistic health practitioners include among their successes the introduction of acupuncture, biofeedback and autogenic techniques in the control of pain; vasodilation, and physiologic effects of several other autonomic systems. A second area of advance centers on the introduction of Eastern approaches to medicine which rely extensively on philosophies that stress balance and integration of the mind and body—such as massage, Tai Chi and meditation. These approaches, while generally unquantified, nevertheless produce detectable changes in the activation level of the reticular system and in the alpha activity of the brain.

The application of techniques not usually associated with therapy, such as dance, visual arts, music and sensory awareness, represents still another area at the threshold of medical practice. Finally, many holistic practitioners promote the incorporation of entire systems of qualitatively different health approaches, such as those embodied by chiropractic, homeopathy and acupuncture as the basis of their practices.

Taken as a whole, these approaches evoke understandable skepticism among more traditional practitioners. Nevertheless, holistic medicine has proved extremely valuable in at least one area: the experimental. Discoveries of the role of *gating* phenomena in the brain, and, indirectly, the identification of endorphins can be attributed in part to investigations triggered by the importation of acupuncture. Biofeedback research has also proved beneficial in treating migraines and hypertension.

Enhanced Patient-Provider Relations

Holistic health encourages a transition away from the patient dependency fostered by traditional medical practices towards self-reliance and responsibility—and where appropriate, self-care. This belief has been held in high regard by a variety of health planners from Marc Lalonde to the late John Knowles because it decreases the financial and medical dependency of patients on the system. It would be a mistake, however, to presume that this approach characterizes the holistic movement itself. A basic precept of the philosophical systems which undergird holistic health, holds that health can be maintained only when the major deleterious effects of environmental and other disturbances have been taken into consideration and where appropriate, neutralized.

Comment

Traditional practitioners should, therefore, not see the intention of the holistic health movement as trying to supplant established patterns of preventive health practices. Indeed, both groups would probably insist that before persons be held fully responsible for their own health, known environmental hazards like lead and pesticides be controlled. Holistic and orthodox practitioners are increasingly aware of the weight which such external forces place on the adaptive abilities of persons, and together these groups can encourage their elimination so that personal health practices can be effective.

Moreover, orthodox practitioners may wish to

incorporate the most valuable techniques that holistic practitioners use into their own. Allergen testing, for instance, in the treatment of migraine headaches or sprue (gluten sensitization) now appears to be a bona fide concomitant of office practice. Whether a similar desensitization can be used for other *brain allergies* identified by holistic practitioners remains to be proved. Similarly, use of herbal preparations which previously have been neglected as old fashioned or simply too faddish might well be reconsidered. For instance, it may make good sense to use the calming and soporific properties of camomile tea for a sick child, rather than the recently proved potentially carcinogenic antihistaminic sleep preparations or cough syrups.

Finally, seeing a health provider's role as helper and information giver rather than as cryptic, medicine dispenser reflects the American ethos of independence, autonomy and self-determination. We would all wish to discourage health approaches that encourage dependence, helplessness and lack of personal responsibility.

Perhaps, like the inhabitants of Thomas Mann's *Magic Mountain,* patients of both holistic and orthodox practitioners may gain the most by learning to see serious illness as a special life experience. Although a radical idea, dying is increasingly being recognized as an important, albeit final, opportunity for growth and transformation. And in less extreme circumstances, a practitioner might improve a patient's well-being by helping him or her to understand, learn from and integrate the experience of healing.

Holistic health has this and probably much more to offer any open-minded physician, nurse or paraprofessional whose perspective on medical practice includes a concern for the integrity of the whole person.

REFERENCES

1. Carlson RJ: Planners and the end of medicine. Am J Health Planning 1:32-37, Jul 1976
2. Huang-Ti Nei Ching: The Yellow Emperor's Canon of Medicine. China 249-221 BC (See Tsuei JJ: Eastern and Western approaches to medicine. West J Med 128:551-557, Jun 1978 for further review of Nei Ching and basic Chinese medical concepts)
3. Scriver CR, Laberge C, Clow CL, et al: Genetics and Medicine: An evolving relationship. *In* Abelson PH (Ed): Health Care: Regulation, Economics, Ethics, Practice. Washington, DC, AAAS:145-150, 1978
4. Terasaki PI: High association of an HL-A Antigen, W27, with Ankylosing Spondylitis. New Engl J Med 288:704-707, 1973
5. Anonymous: HLA disease susceptibility: A primer. N Engl J Med 297:1060-1063, 1977
6. Sweeny GD, et al: Iron deficiency prevents liver toxicity of 2,3,7,8-Tetrachlorodibenzo-p-dioxin. Science 204:332-335, Apr 20, 1979
7. Crow KD: Lipid profiles in dioxin-exposed workers. Lancet 1:982, May 5, 1979
8. Fink DL: Holistic health: Implications for health planning. Am J Health Planning 1:23-31, Jul 1976
9. Blum HL: From a concept of health to a national health policy. Am J Health Planning 1:3-22, Jul 1976

On Healing the Whole Person: A Perspective

RICHARD H. SVIHUS, MD, DrPH

THE TERM holistic health has in a few short years, become nearly a household word. Holistic health centers have appeared like mushrooms, offering various alternative diagnostic and therapeutic modalities. For want of a better description of the nature of their practices, it appears that many alternative practitioners have jumped on a passing bandwagon and have adopted this *new,* ill-defined term to mean whatever their practices happen to be. Because few people appear to know the origin or meaning of the word holistic and because the terms holistic health and whole person are so often misused, this commentary points out the source and original meaning of the concept.

The word holism refers to the concept that any entity is greater in its wholeness than in the sum of its parts. Holistic refers to the state of integration of a person, as a body and a soul, with the spiritual self, making him or her whole.[1,2] Because these terms and concepts derive from biblical Greek, it is necessary to look to the Bible to

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understand the context in which they were originally used.

The word holistic is derived from the Greek word *holos. Holos* means the entirety or completeness of a thing in its wholeness,[3] and is found throughout the *New Testament.*[4] The state of wholeness and of health was very often equated with salvation, so that a person who was made whole, or who was healed, was saved. For example, in the account of the paralytic who was lowered through the roof (Mark 2:1-12), it is stated "Which is easier to say to the paralytic, 'Your sins are forgiven,' or to say, 'Arise, and take up your pallet and walk'?"

The holistic concept is defined by the Apostle Paul (I Thessalonians 5:23): "May the God of peace Himself sanctify you wholly; and may He preserve you whole and entire," (literally, "the whole of you") "in spirit, and in soul, and in body, without blame until the coming of our Lord Jesus Christ." Paul is expressing in this concept that we exist as mutidimensional beings: in spirit (pneuma), the immortal principle and the source of life; in soul (psyche or anima), the seat of emotions and of thoughts, and in body (soma), the flesh created of the dust of the earth.[5]

For "the whole of you" or "whole and entire," Paul uses the Greek word *holokleron,*[6] implying the completeness of a person in all his parts, from his origin at the Godhead, through all dimensions of existence, to his manifestation in a physical body.[3,7] Paul uses the Greek word *holoteles*[6] to denote *wholly,* and to imply that the whole is integrated and brought to completeness and perfection through sanctification.[3] Hence, in the holistic state, the whole being, while multidimensional, is sanctified in its integration, its completeness, its perfection and its wholeness.[7]

While writers of the early Christian church expressed similar concepts,[8] over the centuries interest in the wholeness and integration of our compound nature has subsided. The *Interpreter's Dictionary of the Bible* (1962) contains the following statement:

> Jesus was firmly convinced of his Father's purpose for human wholeness and salvation. . . . Jesus viewed each person as an essential unity of body and mind. This holistic emphasis was as far removed from the Greek concept of body as a prison house for the soul as it was from the outlook of Descartes in a later age. Cartesian philosophy divided the personality into physical and mental categories, considering the latter alone to be the proper sphere of operation of the church.[9]

It appears that Cartesian philosophy furthered the artificial division between physical and spiritual healing, and between science and religion. It must be noted that this artificial separation of body and mind—of things physical and things spiritual—was not part of the teachings of the early Christian church.

The words holistic and holism, as such, first appear to have been used by Jan Smuts in his book, *Holism and Evolution,* published in 1926.[10] Smuts served as a general in the British Army and as prime minister of South Africa.[11] In his book he describes an evolutionary concept in which "holism underlies the synthetic tendency in the universe." Entities growing, developing and evolving become at some point complete in their nature, so that their wholeness becomes greater than the mere sum of their parts. They then move to new levels of being—new *wholes*—brought about by the creative force within, which he calls holism. The whole-making tendency in evolution

> is nothing but the gradual development and stratification of a progressive series of wholes, stretching from the inorganic beginnings to the highest levels of spiritual creation. Wholeness, healing, holiness—all expressions and ideas springing from the same root in language as in experience—lie on the rugged upward path of the universe.[10]

Commenting on the concept of wholeness, Sir William Osler, former Professor of Medicine at Johns Hopkins University, said "The greatest aid in the prevention of disease is to preserve the due proportion of mind and body, for there is no proportion or disproportion more productive of health and disease, and of virtue and vice, than that between soul and body."[12] Osler offers the following quote and comment on passages from Plato's *Dialogues,* " 'Hippocrates, the Asclepiad, says that the nature even of the body can only be understood as a whole.' The importance of healing the whole and not the part is insisted on. 'For this is the great error of our day *(in Hippocrates' time!)* in the treatment of the human body, that physicians separate the soul from the body.' "[12]

Holistic health, then, is a state of integration of the physical body and of the mental and emotional soul-self, in harmony with the spiritual self. This holistic or whole-person concept does not in any way imply an over-emphasis on any one diagnostic or therapeutic modality nor that any person can do anything without training. And it certainly does not intend to imply a cover for

a collection or smorgasbord of questionable and unfounded alternative practices.

Rather, the concept refers to the fact that the whole of a person is greater than the mere sum of his parts, and that there is an approach to the whole person who is ill, instead of merely to his parts or to his illness as if they were separate from the whole of him. Therefore, one can speak of the holistic approach to the patient with cancer,[1,13] for example, instead of an approach to the cancer or to the affected organ.

Whole person does not refer merely to the whole physical body—that is, from head to toe. Rather, the concept adds to the physical body the additional dimensions of the mental and spiritual self (the Apostle Paul's *holokleron*), and implies the treatment of the parts of the person as an integrated whole (the Apostle Paul's *holoteles*).

Most alternative therapies, which may not have been proved effective by scientific methods, must depend in part or entirely on faith for their effectiveness. Faith can be an effective part of the healing process, and probably is the cause of many spontaneous remissions of presumably incurable diseases. (Remember the biblical admonition [Matthew 9:22; Mark 5:34; Luke 8:48, 17:19, 18:42], "Your faith has made you well."[14]) But the danger inherent in alternative therapies is that one may come to believe that the therapies are effective in and of themselves, without taking into account the component of faith. Licensure of alternative practitioners could result in institutionalizing techniques which are therapeutic only when carried out by certain persons who are capable of generating faith on the part of others. One must be careful, therefore, not to read into the concept of the whole person an implication of alternative foolishness which is not there.

Examples of approaching the whole person are hospices for dying patients and their families. The hospice concept has become very popular in the United States, following its beginnings in Britain, and has been endorsed by various state medical associations[15] and the American Medical Association.[16] The variety and functioning of hospice programs are well described elsewhere.[17-22] Markel and Sinon, of the American Cancer Society, state "The hospice program is a humane, holistic approach to medical care that has great support among all elements of society." They define hospice as a physician-directed health care delivery program of coordinated services which "employs a multi-faceted approach: narcotic and non-narcotic analgesics are used in physical symptom control, and the interdisciplinary hospice team provides psychologic, sociologic, and spiritual services as they are needed. The patient *and* family is the primary unit of care. . . ."[23]

The hospice concept then, involves coordinated care for the patient's physical body during the dying process. But the program also involves concern for the mental and emotional well-being of both the patient and his family in their adjustment to the reality of death, in their education for the care of the patient during the dying process and in their making practical arrangements for the death, the funeral and the care of those surviving. Under the guidance of clergy, the hospice concerns itself with the spiritual and religious needs of the patient and family, such as their fear of dying, their concerns regarding their relationship with their Creator, and their guilt and anxiety over wrongs done to others and to each other. By this multidisciplinary and multidimensional approach, the dying patient is viewed and cared for as a whole person.

It is unfortunate that a person must wait until he is dying before he can partake of a health care program that treats him as a whole rather than as organs and diseases. There is need for a concept of the hospice for the living, in which, in the words of Hippocrates (as quoted by Osler) "The importance of healing the whole and not the part is insisted on."[12]

We must retain and make full use of the great scientific advances we have achieved in the treatment of our physical bodies. But to this knowledge of the chemistry and physiology of disease should be added the education of and understanding by the patient to assume responsibility for his own life-style and health habits and to gain insights into his emotions and feelings and their role in health and disease. A patient should be treated as a person and not just as a bag of chemicals or as the "gall bladder waiting in X-ray." The soul of each person has an existence just as does the physical body, and the great error of our day, just as in Hippocrates' time, is that "physicians separate the soul from the body."[12] Man does not exist apart from his Creator, and the spiritual side of man should be involved in the healing process.

The clergy have an important role to play in the healing of the whole person, perhaps more vital than many hospital chaplains and physicians fully realize. For healing is not an affair just of the physical body; rather, it is as much related to one's capacity to give and to receive love as it is to the ministrations of the physician. While physicians may rearrange tissues, balance chemicals and kill bacteria, the real healing of the body comes from within the person and is related to the soul-body interaction. As Sir William Osler so astutely observed, "there is no proportion or disproportion more productive of health and disease . . . than that between soul and body."[12]

The concept of the healing of the whole person, or holistic medicine, is not new—in fact, as has been shown, it is ancient. It entails approaching each patient as a physical body, a mental and emotional self, and a spiritual being (expressed by the biblical Greek word *holokleron*); it entails treating each patient as an integrated whole (expressed by the Greek *holoteles*), and it entails faith in relying on the healing from within to manifest itself. In many instances it may not be acceptable, practical or economical to implement fully the concept of healing of the whole person. Certainly experimentation, clinical experience and much understanding and cooperation will be needed in order that practical approaches to treating persons in their wholeness, such as a concept of hospice for the living, may become a reality.

REFERENCES

1. Svihus RH: The concept of holistic health: Origins and definitions. (Transcript of a presentation to the "Healing Center of the Future Conference," San Diego, Sep 1976.) J Holistic Health 2:17-21, 1977
2. Svihus RH: The dimensions of wellness: The holistic viewpoint. Am Holistic Med 1:19-25, Feb 1979
3. Thayer JH: Greek-English Lexicon of the New Testament. Grand Rapids, MI, Zondervan (repr 1976), pp 443-444
4. Darton M (Ed): Modern Concordance to the New Testament. Garden City, NY, Doubleday & Co, 1976, pp 661-662
5. Clarke A: Clarke's Commentary, Vol 6. Nashville, TN, Abingdon Press (repr 1977), p 555
6. Marshall A: The RSV Interlinear Greek-English New Testament. Grand Rapids, MI, Zondervan, 1958, p 813
7. Vine WE: An Expository Dictionary of New Testament Words. Old Tappan, NJ, Revell Co, 1940, pp 213-214
8. Origen: De Principiis, *In* Ante-Nicene Fathers, Vol 4, Grand Rapids, MI, Eerdmans (repr 1976), pp 239-384
9. Harrison R: Healing, health, *In* Interpreters Dictionary of the Bible, Vol 2. Nashville, TN, Abingdon Press 1962, pp 541-548
10. Smuts JC: Holism and Evolution. London, Macmillan, 1926; repr Westport, CT, Greenwood Press, 1973
11. Smuts JC: *In* Encyclopedia Americana, Vol 25. New York, Americana Corp, 1978, pp 81-82
12. Osler W: Aequanimitas With Other Addresses. Philadelphia, Blakiston, 1914
13. Fiore N: Fighting cancer—One patient's perspective. N Engl J Med 300:284-289, Feb 8, 1979
14. Darton M (Ed): Modern Concordance to the New Testament. Garden City, NY, Doubleday, 1967, pp 46-50
15. Klutch M: Hospice for terminally ill patients—The California experience. West J Med 129:82-84, Jul 1978
16. 'Hospice' concept wins endorsement. Am Med News, Jun 30/Jul 7, 1978, p 10
17. The hospice story in California: Report of the Committee on Evolving Trends in Society Affecting Life. San Francisco, Calif Med Assoc, Jul 1978
18. Holden C: Hospices: For dying, relief from pain and fear. Science 193:389-391, Jul 30, 1976
19. Craven J, Wald FS: Hospice care for dying patients. Am J Nursing 75:1816-1822, Oct 1975
20. Liegner LM: St. Christopher's Hospice, 1974—Care of the dying patient. JAMA 234:1047-1048, Dec 8, 1975
21. Shephard D: Principles of practice of palliative care. Can Med Assoc J 116:522-526, Mar 5, 1977
22. Stoddard S: The Hospice Movement—A Better Way of Caring for the Dying. New York, Random House, 1978 (Originally published by Stein & Day, New York, Mar 1978)
23. Markel WM, Sinon VB: The hospice concept. CA 28:225-237, Jul/Aug 1978 (Available as a reprint from the American Cancer Society, New York, NY, Monograph #3403)

Holistic Medicine: From Pathology to Prevention

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SINCE THE MIDDLE AGES humankind has been divided into separate aspects of body, mind and spirit. This split is still evidenced in the present structure of the healing professions. Physicians are dedicated to the treatment of the body; psychologists and psychiatrists are concerned with treating the mind, and yet a third group, the clergy, is attendant to spiritual healing. Such fragmentation and specialization is a relatively recent phenomenon. More unified concepts of health and disease extend further back to the roots of medicine in the late Assyrian civilization, and in the Greek culture as exemplified in the writings of Hippocrates and Aristotle, who clearly

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observed the effects of emotions on physical disease. Despite this early principle of a psychosomatic dimension inherent to medicine, Coulter's[1] three-volume work, *Divided Legacy,* has traced a progressive division between body, mind and environment characteristic of the rationalist school as contrasted to a more integrated or empirical approach. Within the healing professions today, there is a reemphasis on the empirical school characterized by such a holistic approach to each person. Holistic medicine addresses biological, psychosocial and environmental factors, emphasizing prevention of disease and maintenance of optimum health rather than solely the treatment of disease.

Throughout the history of medicine, practitioners have puzzled about the seemingly inexplicable recovery of mortally ill patients and the sudden morbidity of patients who should have fully recovered. Beginning as early as the 19th century, the French neurologist Charcot explored the psychosomatic causes of hysterical seizures. This research was followed by that of Freud, Jung, Sherrington, Dunbar, Pavlov, Cannon, Selye and others who began to define the precise neurophysiological mechanisms and biochemical mediators by which psychological states and environmental influences held profound sway over the body. Most recently, cardiologists Friedman and Rosenman[2] defined the type A personality predisposed toward cardiovascular disorders, and there has been a resurgence of research, as noted in *Science,* to study possible psychosomatic factors involved in cancer.[3] Among the most striking research is a longitudinal, prospective study of 1,337 medical students by Thomas.[4] Her research, spanning 1948 to 1964, focused on the prospective personality profiles which were to correlate later with suicide, mental illness, hypertension, coronary heart disease and malignant tumors. From the longitudinal data, the pathogenic personalities that emerged as most distinct were those of students in whom malignant tumors later developed. While issues of causality require further research, factors such as stress and psychosocial influences cannot be dismissed in any comprehensive inquiry. There is no inherent antagonism between purely biomedical approaches to health and disease and the consideration of psychosocial influences characteristic of holistic medicine. In a most concise article, Engel[5] proposed such an integration as the basis for "a new medical model" with responsibilities shared equally among diverse health professionals and patients.

In moving from basic research issues to institutional considerations, Knowles[6] has described the present situation most succinctly:

> I believe the idea of a "right" to health should be replaced by that of a moral obligation to preserve one's own health. The individual then has the "right" to expect help with information, accessible services of good quality, and minimal financial barriers. Meanwhile the people have been led to believe that national health insurance, more doctors, and greater use of high-cost, hospital-based technologies will improve health. Unfortunately, none of them will.

These beliefs have been reiterated by McNerney, Dubos, McKeown and Saward, and Ingelfinger[7] who estimated the capacity of purely biomedical approaches to achieve health for the population as "marginally on the positive side of zero." Basic research, health practitioners and health care institutions have reached the limits of a purely biomedical, technological approach to health care and need to extend their efforts to include holistic medicine.

Complex issues cannot be adequately addressed here but it is possible to provide a brief list of the innovative areas characteristic of holistic medicine. Many items have been noted in the *Health of Canadians* issued by Lalonde[8] when he served as the Minister of Health in Canada. Holistic medicine is characterized by the following: (1) Health is not a subspecialty of medicine but requires cooperative efforts of physicians, psychologists, environmentalists and other persons working together on an equal basis.[9,10] (2) Preventive care with an emphasis on health maintenance can be shown to be cost effective.[11,12] (3) Methods of maintaining health are the prerogative of each person and his or her life-style rather than of medicine per se, and the subsequent model is one of education rather than of diagnosis and treatment of disease.[13] (4) Psychosocial and biochemical factors are weighted equally with an emphasis on etiology.[14,15] (5) An awareness of one's bodily and mental states and the factors affecting them is critical in determining the balance between health and illness,[16] and life and death.[17] (6) Optimum health is based on the management of stress,[18,19] as well as on dietary and nutritional factors,[20] regular physical activity[21] and a sound physical[22,23] and psychosocial environment. (7) Self-regulatory methods founded on empirical research indicate the capacity of persons to become

responsible participants in the healing process through clinical biofeedback,[24] autogenic training, Jacobson's system of progressive relaxation and meditation.[25] (8) Use of terms such as *placebo response*[26] (shown to elicit a biochemical response[27]), *spontaneous remission* and *psychosomatic* tend to dismiss major factors in health care which need to be researched in greater depth. (9) With the elimination of all disease, human life expectancy would be increased by perhaps ten years, and further research needs to explore the biologic potential which is considerably longer.[28,29] (10) Health is approximately 90 percent dependent on the above factors which are beyond the province of biomedical technology as noted by McKeown,[30] Illich,[31] Palmer and many analysts. If the prevention of disease and the attainment of optimum health are the ultimate goals of the health professions, then holistic medicine requires the equal responsibility and cooperation of the public, health practitioners and institutions.

Many of these issues and references are explored more systematically in *Mind as Healer, Mind as Slayer*[19] and in *Holistic Medicine*.[32] At present, holistic medicine is more suggestive of a direction than an accomplished fact. Humanitarian concerns amidst the proliferation of biomedical technology and economic imperatives issued by the Federal Trade Commission[33] and Blue Cross have converged to create the necessity of a profound evolution in health care. For Hippocrates, Aristotle and Paracelsus *physis* represented an innate healing capacity to be elicited and sustained for optimum health. Holistic medicine is a relatively recent manifestation consistent with this fundamental quest of all humankind.

REFERENCES

1. Coulter HJ: Divided Legacy—A History of the Schism in Medical Thought. Volumes 1, 2, and 3. Washington, DC, Wehawken Book Co., 1977

2. Friedman M, Rosenman RH: Type A Behavior and Your Heart. New York, Alfred A. Knopf, 1974

3. Holden C: Cancer and the mind—How are they connected? Science 200:1363-1369, Jun 23, 1978

4. Thomas CB, Duszynski KR: Closeness to parents and the family constellation in a prospective study of five disease states—Suicide, mental illness, malignant tumor, hypertension and coronary heart disease. John Hopkins Med J 134:251-270, May 1974

5. Engel GL: The need for a new medical model—A challenge for biomedicine. Science 196:129-136, Apr 8, 1977

6. Knowles JH: The responsibility of the individual. Science 198:Masthead page, Dec 16, 1977

7. Ingelfinger FJ: Health: A matter of statistics or feeling [Review of *The Role of Medicine: Dream, Mirage, or Nemesis* by Thomas McKeown] (Editorial). N Engl J Med 296:448-449, Feb 24, 1977

8. Lalonde M: A New Perspective on the Health of Canadians. Ottawa, Minister of National Health and Welfare Information, 1975

9. Breslow L: A quantitative approach to the World Health Organization definition of health, physical, mental and social well-being. Int J Epidemiol 1:347-355, Winter 1972

10. Carlson RJ: The End of Medicine. New York, John Wiley & Sons, 1975

11. Kristein MM, Arnold CB, Wynder EL: Health economics and preventive care. Science 195:457-462, Feb 4, 1977

12. Farquhar JW: The American Way of Life Need Not Be Hazardous to Your Health. Stanford, CA, Stanford Alumni Association, 1978

13. Ng LKY, Davis DL, Marderscheid RW: The Health Promotion Organization—A Practical Intervention Designed to Promote Health Living. Public Heath Rep 93:446-455, Sep-Oct 1978

14. Engel GL: The need for a new medical model—A challenge for biomedicine. Science 196:129-136, Apr 8, 1977

15. Saward E, Sorensen A: The current emphasis on preventive medicine. Science 200:889-894, May 26, 1978

16. Cousins N: Anatomy of an illness—As perceived by the patient. Saturday Review, pp 4-51, May 28, 1977

17. Simonton OC, Matthews-Simonton S, Creighton J: Getting Well Again. Los Angeles, J. P. Tarcher, Inc., 1978

18. Selye H: The Stress of Life. New York, McGraw-Hill, 1956

19. Pelletier KR: Mind as Healer, Mind as Slayer—A Holistic Approach to Preventing Stress Disorders. New York, Delacorte and Delta, 1977

20. Ballentine R: Diet and Nutrition—A Holistic Approach. Honesdale, PA, The Himalayan International Institute, 1978

21. Cooper KH: The Aerobics Way. New York, M. Evans and Co., 1977

22. Becker RO: Boosting Our Healing Potential, *In* Science Yearbook, Chicago, World Book Encyclopedia, 1975, pp 40-55

23. Randolph TG: Specific adaptation. Ann Allergy 40:333-345, May 1979

24. Aldine Publishers: Biofeedback and Self-Control. Annual Volumes 1970-1978. Chicago, Aldine Publishers

25. Bloomfield HH, Kory R: The Holistic Way to Health and Happiness. New York, Simon and Schuster, 1978

26. Benson H, Epstein HD: The placebo effect—A neglected asset in the care of patients. JAMA 232:1225-1227, Jun 23, 1975

27. Levine JD, Gordon N, Fields HL: The mechanism of placebo analgesia. Lancet 2:654-657, Sep 23, 1978

28. Leaf A: Youth in Old Age. New York, McGraw-Hill, 1975

29. Finch CE, Hayflick L: The Biology of Aging. New York, Van Nostrand Reinhold Co., 1977

30. McKeown T: The Role of Medicine—Dream, Mirage, or Nemesis. London, Nuffield Provincial Hospital Trust, 1976

31. Illich I: Medical Nemesis—The Expropriation of Health. New York, Pantheon, 1976

32. Pelletier KR: Holistic Medicine—From Stress to Optimum Health. New York, Delacorte and Delta, 1979

33. FTC gaining allies in attack on MDs. Medical World News, Jan 8, 1979, p 13

Holistic Health Care and California's Board of Medical Quality Assurance

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ALTHOUGH IT IS impossible to offer a definition of holistic health care on which all will agree, it is possible to agree on certain features. One such feature is the strong holistic emphasis on individual freedom of choice in treatment, conventional or otherwise. In this respect, the holistic and consumer movements are similar. It is, perhaps, this consumer orientation that best explains the special interest of the California State Board of Medical Quality Assurance in holistic health care: the Board is, after all, administratively a part of the state's Department of Consumer Affairs, and more than a third of its members are nonphysicians or public members.

The Board's concern over the issue of freedom of choice is reflected in its recent action regarding the California Senate Bill No. 1011 (Campbell), a bill which would have removed the present requirement that new therapies be efficacious as well as safe. The Board is under some obligation to take a position, in support or in opposition, of bills that would affect its duties, as this one certainly would. After a motion to disapprove the bill failed, a motion to approve it was one vote short of the majority necessary to carry. The support of nearly half of the Board's members reflects a strong conviction that the choices open to the public should not be limited only to conventional treatments sanctioned by the medical establishment.

The holistic health movement offers practical as well as conceptual challenges to the Board. The legal definition of the practice of medicine in the state of California states that

> Any person, who practices or attempts to practice, or who advertises or holds himself out as practicing, any system or mode of treating the sick or afflicted in this State, or who diagnoses, treats, operates for, or prescribes for any ailment, blemish, deformity, disease, disfigurement, disorder, injury or other mental or physical condition of any person, without having at the time of so doing a valid, unrevoked certificate as provided in this chapter, or without being authorized to perform such act pursuant to a certificate obtained in accordance with some other provision of law, is guilty of a misdemeanor. (Section 2141 of the Business and Professions Code)

This definition has been criticized for its broad language. It was the legal basis for the arrest of a health food store operator in Sacramento last year for practicing medicine without a license. Her offense was giving nutritional advice to her patrons. It is hardly surprising, therefore, that increasing numbers of health professions have recently sought legal protection (such as state licensure) for practicing their art. Physicians' assistants and acupuncturists have been the most recent groups of health professionals to have their modes of practice legally defined, sanctioned and integrated with traditional medical practice.

Should holistic practitioners, most of whom are unlicensed at present, be added to this list? Some holistic practitioners are attempting independently to define the scope of their various practices, to articulate a code of ethics, and to explore alternatives to licensure, including certification, which might protect them from prosecution for illegally practicing medicine. Among the obstacles faced in this effort in California is the fact that there is, at present, no coordinated and explicit State policy on new health manpower categories. Until such a policy is adopted, the Division of Allied Health Professions of the Board of Medical Quality Assurance has taken the position of disapproval of any new licensing categories.

Refer to: Bunker JP, Gerber WG: Holistic health care and California's Board of Medical Quality Assurance. *In* Orthodox medicine, humanistic medicine and holistic health care—A forum. West J Med 131:484-485, Dec 1979

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At present, the Board is seeking private funding for a proposed two-year study of the legal definition of the practice of medicine in an effort to clarify the licensing dilemma. The study will examine the roles of patients, providers and government in promoting health, and how they are affected by Section 2141 of the Medical Practices Act. Among specific questions to be asked are the following: Does Section 2141 needlessly restrict alternative modes of health care? Does Section 2141 needlessly infringe upon persons' rights to the treatment of their choice? Does it enhance patients' rights?

Pending completion of the study, and the enactment of legislative remedies that may be appropriate, the Board must, of course, continue in its attempt to interpret and apply current law. In doing so, the Board must also consider its broader responsibilities to protect the public's health. These responsibilities, in turn, should be viewed from the perspective of current epidemiologic evidence on the determinants of health and longevity. Within this perspective, it is sobering to note that holistic health care, if defined to include all those determinants other than the practice of medicine, surely contributes a larger positive effect than does the practice of medicine itself. This is not to say that the practice of medicine is not an extremely important contributor to health and longevity. But, it does mean that the contribution of other factors, such as nutrition, life-style and the environment, over which the holistic practitioner makes some claim, is greater. And it is not to say that the holistic movement may not open the door to quackery by some; it certainly does.

There are those who assert that holistic health care encompasses alternative methods of healing from which traditional medicine is, by definition, excluded. Others maintain that efforts to integrate holistic health care and traditional medicine are at least premature, and that more time is required for the holistic movement to establish itself. But if holistic health care and humanistic medicine are seen as extending the areas of responsibility or the horizons of medicine to include all of these other determinants, and if we bend our energies to integrate the many members of society, at whatever level, working towards this goal, the public and its health will surely be better served.

Leon Eisenberg has recently written

> If the twin goals of improving the public's health and reducing the demand for medical care are to be attained, three kinds of efforts are required: (1) research in educational methods must be undertaken to encourage health-promoting behavior; (2) biological research must be fostered for disease prevention; and (3) social innovation must be attempted on a new scale if a more humane society is to be created. . . . As physicians, our daily practice with human ailments makes us aware of the extent to which problems of ill health flow from failures in our political, economic, and social institutions.[1]

Seen within this broader context, holistic health care is simply one component of a broad social effort to improve both the public's health and its quality of life. Let us encourage its practitioners in their search for productive roles.

REFERENCE

1. Eisenberg L: The search for care. Daedalus, Winter 1977, pp 235-246

Refer to: Weitzman RE, Kleeman CR: The clinical physiology of water metabolism—Part II: Renal mechanisms for urinary concentration; diabetes insipidus (Medical Progress). West J Med 131:486-515, Dec 1979

The Clinical Physiology of Water Metabolism

Part II: Renal Mechanisms for Urinary Concentration; Diabetes Insipidus

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CHARLES R. KLEEMAN, MD, *Los Angeles*

The renal reabsorption of water independent of solute is the result of the coordinated function of the collecting duct and the ascending limb of the loop of Henle. The unique juxtaposition of the ascending and descending portions of the loop of Henle and of the vasa recta permits the function of a countercurrent multiplier system in which water is removed from the tubular lumen and reabsorbed into the circulation. The driving force for reabsorption is the osmotic gradient in the renal medulla which is dependent, in part, on chloride (followed by sodium) pumping from the thick ascending loop of Henle. Urea trapping is also thought to play an important role in the generation of a hypertonic medullary interstitium. Arginine vasopressin (AVP) acts by binding to receptors on the cell membrane and activating adenylate cyclase. This, in turn, results in the intracellular accumulation of cyclic adenosine monophosphate (AMP) which in some fashion abruptly increases the water permeability of the luminal membrane of cells in the collecting duct. As a consequence,

Renal Regulation of Water

THE ANATOMIC AND PHYSIOLOGIC concepts on which we based our earlier discussion[143(p1459)] of the kidney's maximal concentrating and diluting capacity have been confirmed and broadened by continuing investigations, and the results of these investigations have been analyzed and summarized recently in excellent reviews.[144-148] Improved microdissection, microperfusion, micropuncture and microchemical techniques, combined with transmission and scanning electron microscopy used in these studies, have contributed to a better understanding of water excretion in normal humans and in those with various disorders.

Physiologic Anatomy

The nephrons of a mammalian kidney arise from the intralobular arteries and their afferent arterioles at varying depths within the cortex of the kidney, and are varying lengths. Their length

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water flows along an osmotic gradient out of the tubular lumen into the medullary interstitium.

Diabetes insipidus is the clinical condition associated with either a deficiency of or a resistance to AVP. Central diabetes insipidus is due to diminished release of AVP following damage to either the neurosecretory nuclei or the pituitary stalk. Possible causes include idiopathic, familial, trauma, tumor, infection or vascular lesions. Patients present with polyuria, usually beginning over a period of a few days. The diagnosis is made by showing that urinary concentration is impaired after water restriction but that there is a good response to exogenous vasopressin therapy. Nephrogenic diabetes insipidus can be identified by a patient's lack of response to AVP. Nephrogenic diabetes insipidus is caused by a familial defect, although milder forms can be acquired as a result of various forms of renal disease. Central diabetes insipidus is eminently responsive to replacement therapy, particularly with dDAVP, a long lasting analogue of AVP. Nephrogenic diabetes insipidus is best treated with a combination of thiazide diuretics as well as a diet low in sodium and protein.

is dependent on the length of the loop of Henle (Figure 22). The loop of Henle consists of the straight portion of the proximal tubule (pars recta), the thin limb, with descending and ascending segments, the ascending thick segment and a short straight portion of the distal tubule (pars recta) proximal to the macula densa. Basically, all nephrons in the mammalian kidney can be divided into two kinds: the outer cortical nephron with its short loop of Henle consisting of abbreviated thin limb segments penetrating, at most, to the inner strip of the outer zone of the medulla (Figure 22), and the juxtamedullary nephron with its long loop of Henle consisting of well-developed descending and ascending thin segments which traverse the entire medulla and form their pin loops at varying depths within the inner medullary zone. The larger the number of these nephrons and the longer their loops of Henle, the greater is the concentrating capacity of the animal.*

In humans,[144,146] it has been estimated that there are approximately 1 million nephrons in each kidney and that approximately 15 percent of the nephrons have long loops of Henle.[144,148] Of course, descending from the outer cortex to the juxtamedullary zone, there may be grada-

*While this relationship holds for most mammalian kidneys[144] there are some striking exceptions. The macaque monkey, while capable of forming concentrated urine well above 1,000 mOsm per kg during fluid deprivation, has virtually no inner medulla or long loops of Henle. Other exceptions are the mountain beaver and the chinchilla.[144]

ABBREVIATIONS USED IN TEXT

AVP = arginine vasopressin
cAMP = cyclic adenosine monophosphate
C_{H_2O} = free water clearance
DI = diabetes insipidus
GFR = glomerular filtration rate
NDI = nephrogenic diabetes insipidus
PGE = prostaglandin E
U/P = urine to plasma (ratio)

tions or variations between the two basic types of nephrons depending on their relative positions in the cortex.[148] In general, the pars recta changes to the thin descending limb at the outer strip of the outer medullary zone and the thick segment of the ascending limb is located in the outer medullary zone. The segment of the thick ascending limb of the loop of Henle, which begins at the point where it crosses from outer medulla to the cortex and extends to the macula densa, is called the cortical diluting segment, the cortical portion of the thick ascending limb or the straight (pars recta) segment of the distal tubule. The proximal and distal *convoluted* tubules of all nephrons are confined to the isotonic cortex where the distal convoluted tubule terminates or becomes the unbranched cortical collecting duct. The latter traverses the cortex to the junction with other cortical collecting tubules near the corticomedullary or outer strip of the outer medullary zone where it forms the medullary collecting duct which, in turn, traverses the entire medulla and enlarges to terminate at the duct of Bellini near the tip of the medullary pyramid.

The blood supply of the renal medulla is composed entirely of postglomerular vessels derived from the juxtamedullary glomeruli. These vessels (vasa recta) descend into the medulla, take a hairpin turn, and ascend to their level of origin. These vascular loops (capillaries) lie in the closest proximity with the loop of Henle and collecting ducts (Figure 22). However, Kriz and Lever[149] described a tubulovascular relationship that must be of functional importance. The descending limb is juxtaposed to both descending and ascending vasa recta, while the ascending thin limb is adjacent to the collecting duct. The descending vasa recta, at various levels in the medulla, gives off branches that form a capillary plexus which surrounds the ascending limb and collecting duct, with blood flowing in a descending direction concurrent to collecting duct and

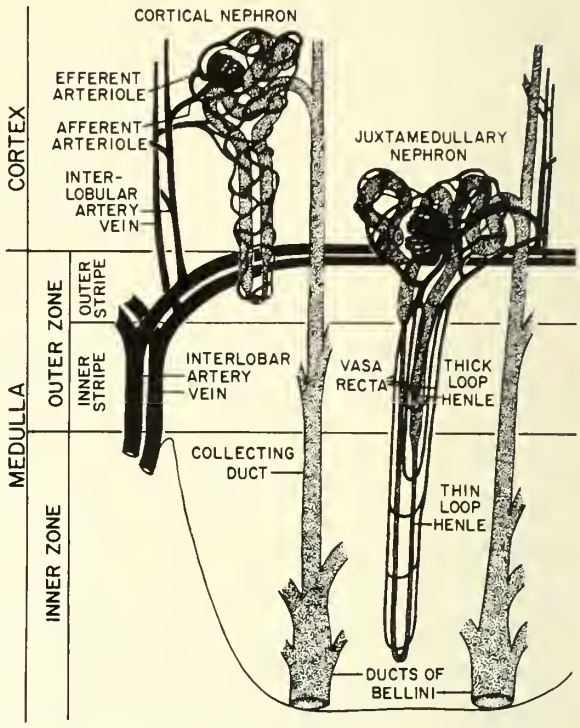

Figure 22.—Diagrammatic representation of the cortical and juxtamedullary nephrons and their vascular supply. (From Pitts RR: Physiology of the Kidney and Body Fluids, 3rd Edition. Copyright © 1974 by Year Book Medical Publishers, Inc., Chicago. Used by permission.)

countercurrent to the ascending limb. As emphasized by Rector,[144] this juxtaposition of limbs, collecting ducts and capillaries suggests that various elements are not exchanging equally with well-mixed interstitium and, therefore, constitute a countercurrent multiplier and exchanger system and, further, that none of the present models takes full consideration of these unique anatomic features.

The loop of Henle (functioning as a countercurrent multiplier system) *creates* the hypertonicity of the renal medulla, essential to the production of a hypertonic urine, whereas the vascular loop (acting as a countercurrent exchanger) *prevents* the dissipation of the hypertonic gradient of the medulla. Throughout the entire nephron, the fundamental processes involved in the production of a dilute and concentrated urine are the active reabsorption of sodium chloride (NaCl) and the variable permeability of the nephron to the passive back diffusion of water and urea along their concentration gradients (Figure 23), the only possible exception being the passive permeability of the thin ascending segment of loop of Henle to salt.

Solute and Water Reabsorption in the Nephron

In the average adult approximately 100 ml of glomerular filtrate is presented to the proximal tubules every minute. During its passage through this water-permeable segment (proximal convoluted and pars recta), approximately two thirds to three fourths of the glomerular ultrafiltrate is reabsorbed into the bloodstream. In this reabsorption process, the tubule fluid remains isosmotic with respect to plasma and there is usually no transepithelial concentration gradient for sodium. Therefore, the amount of isosmotic fluid delivered into the loop of Henle is dependent upon the filtered solute load and on the amount of solute reabsorbed in the proximal tubule. The fluid entering the descending limb of the loop of Henle becomes progressively more concentrated as it approaches the tip of the loop; as it moves up the ascending limb it becomes increasingly dilute until it enters the distal convoluted tubule as a distinctly hypotonic (150 to 200 mOsm per liter) fluid (Figure 23). These basic changes in the loop of Henle, while they may be modified from a quantitative point of view, occur under all circumstances regardless of the volume and composition of the final urine. This is the consequence of the unique transport and permeability characteristics of the loop of Henle which allow it to function as an efficient countercurrent multiplier system, the latter being primarily responsible for our capacity to produce a maximally hypertonic urine.

In recent years the countercurrent hypothesis as applied to mammalian nephrons has been subjected to the most rigorous experimental verification and new models have been formulated to reconcile the observed facts. Many reviews have been published[144-148] and we have drawn most heavily on the very lucid study of Jamison and Maffly[146] for our discussion.

Before discussing these investigations, which have greatly enhanced our understanding of the function of the loop of Henle, it will be helpful to review the concepts of countercurrent flow that enabled the physical chemist Werner Kuhn to recognize the fundamental implications of the U-shaped configuration of the long loops in which fluid flows in opposite directions in adjacent limbs.[146] With respect to heat exchangers, he was well aware that large temperature gradients can be established in the longitudinal axis of such channels while the temperature differences between them at any given horizontal level can be very small. He applied this concept to the concentration or osmotic pressure differential in the loop of Henle and concluded that here, too, small differences in concentrations between ascending and descending limbs, at any given transverse level, could be responsible for great differences

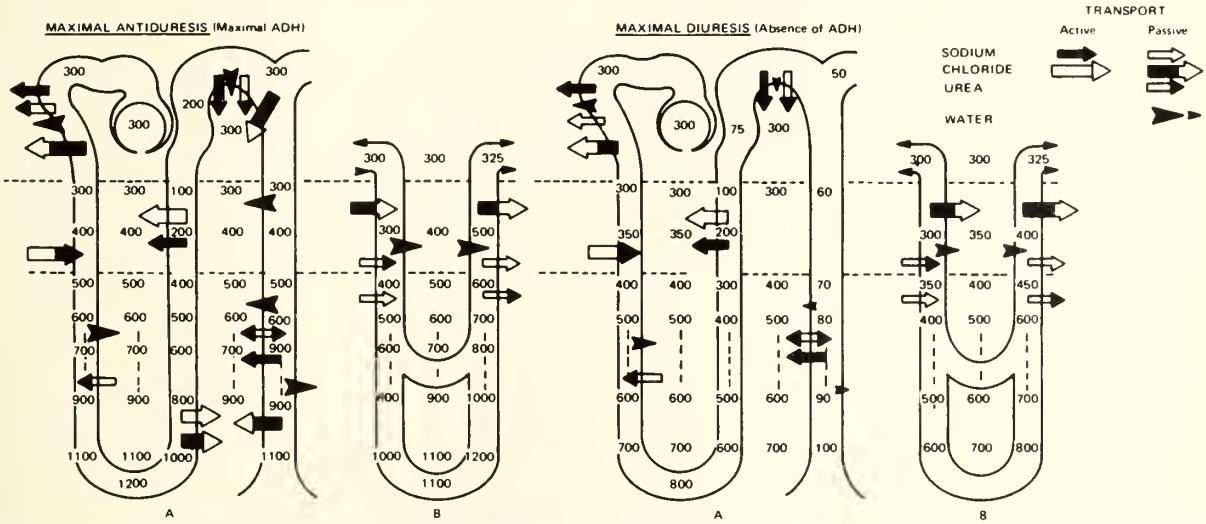

Figure 23.—Countercurrent mechanism as it is believed to operate in the juxtamedullary nephron (A) and vasa recta (B). The numbers represent illustrative osmolality values during maximal antidiuresis (left) and maximal diuresis (right). No quantitative significance is to be attached to the number of arrows; only net movements are indicated. As with the vascular loops, not all loops of Henle reach the papillary tips and, hence, the fluid in them does not become so concentrated as that of the final urine, but rather only as concentrated as the medullary interstitial fluid at the same level. ADH = antidiuretic hormone. (Modified with permission from Gottschalk & Mylle: Am J Physiol 196:927, 1959.)

in solute concentration along the long axis of the tubules and in the surrounding adjacent interstitial tissue.

For such a system to function as a countercurrent multiplier, Kuhn proposed three basic requirements: (1) countercurrent flow, (2) differences in permeability between the tubules carrying fluid in opposite directions and (3) a source of energy. The loop of Henle provides the countercurrent flow, the descending limb has a very high level of permeability to water while the thin and thick ascending limbs are almost impermeable to water,[144,150] and the active transport of NaCl out of the thick ascending limb to surrounding interstitium provides the basic energy source.[144,146]

The impermeability of this latter segment to water means that the concentrations of NaCl transported into the surrounding interstitium must be distinctly hypertonic while the intraluminal NaCl concentration, at this level of the ascending limb, will be hypotonic. As the isotonic fluid from the pars recta of the proximal tubule enters the highly water-permeable descending limb of the loop of Henle, it becomes hypertonic as it loses water to the more concentrated (hypertonic NaCl) surrounding medullary interstitium. As it rounds the bend of the loop, and ascends, this intraluminal fluid—now considerably more concentrated (hypertonic) with respect to NaCl—is presented to the active transport site and pumped into the surrounding medullary interstitium, thereby elevating the NaCl concentration and osmolality of the interstitial tissue to an even higher degree of hypertonicity. Thus, the active transport process in the water-impermeable thick ascending limb, when augmented or *multiplied* by the countercurrent flow in the loop and the continued osmotic flow of water out of the descending limb, results in the very large concentration difference in the longitudinal axis of the medulla between the isosmotic fluid entering the descending limb and the most hypertonic fluid at the tip of the loop and adjacent papillary interstitium (Figure 23). Note that this whole process, initiated by the active transport of NaCl into the outer medulla, occurs without the need to create a transepithelial concentration gradient for NaCl exceeding 100 mEq or 200 mOsm in the horizontal plane at any level of the medulla. "One of the most compelling features of the countercurrent mechanism is its biologic economy. When the urine is hyperosmotic, at no point along the renal tubule does the transepithelial osmotic gradient exceed 200 mOsm per kilogram of water."[146]

As noted in Figure 23, the newly created hypotonic fluid (150 to 200 mOsm per liter) in the thick ascending limb enters the distal convoluted tubule. As it flows from this cortical segment into the cortical and medullary collecting ducts, its concentration is determined primarily by the level of arginine vasopressin (AVP) in the surrounding capillaries. When the amount is sufficient to create maximal permeability of the collecting ducts and, probably, the terminal portion of the distal convoluted tubule, the luminal fluid is reabsorbed until osmotic equilibrium is achieved with the surrounding isotonic cortical or increasingly hypertonic medullary interstitium. Therefore, the most concentrated urine equal to the osmolality of the interstitial fluid or the innermost medulla or papillary tip is created. Lesser amounts of AVP acting on the nephron create less than maximally concentrated urine.

Essential prerequisites of the process described above appear to be an active reabsorption of salt *throughout* the ascending limb and that the fluid

TABLE 6.—*Brief Summary of Permeability Characteristics of Different Segments of the Nephron (Rabbit)**

Segments of Nephron	*Water*	*Sodium Ions*	*Urea*
Descending limb	Very permeable	Impermeable†	Impermeable†
Thin ascending limb	Impermeable	Very permeable	Moderately permeable
Thick ascending limb	Impermeable	Very permeable active chloride pump	Impermeable
Distal tubule (or cortical collecting duct, or both)	Permeable with AVP	Partial sodium-potassium exchange	Impermeable
Medullary collecting duct	Permeable with AVP	Moderately permeable†	Impermeable except at collecting-duct junctions in inner medulla

AVP = arginine vasopressin

*Modified from Britton et al.[156]
†Varies with different species.

in this segment be rendered definitely hyposmotic to the adjacent interstitium. The low-level permeability to the osmotic flow of water has been clearly shown for both the thin and thick ascending limbs[144,150] and there is unquestioned active reabsorption of salt in the thick ascending limb.[144,146] However, studies *in vitro* of the thin segment have failed to disclose any evidence of active transport of sodium or chloride.[150] The contrast between the organelle-rich cuboidal epithelium of the thick ascending limb and the organelle-poor squamous epithelium of the thin ascending limb is consistent with this difference in active salt transport.[148]

If the *in vitro* studies of the transport and permeability characteristics of the *entire* ascending limb did not fulfill the essential prerequisites, how then could we explain the highly efficient countercurrent multiplier system obviously existing in the inner medulla and producing the most hypertonic interstitium at the tip of the pyramid?

This dilemma may have been solved by the proposed models of Stephenson[151,152] and Kokko and Rector[153] which showed that *passive* transport of salt from lumen to interstitium of the thin ascending limb in the inner medulla could be brought about if certain assumptions about relative impermeabilities of various nephron segments to water, salt and urea were made. These impermeabilities have been observed[150,154-156] and are presented in Table 6.

Furthermore, the models allowed the active transport of NaCl to be confined to the thick ascending limb, they provided a clear explanation for the role of urea in augmenting the urinary concentrating ability, and they explained the early important observations of Ullrich and Jarausch[157] that the sodium concentration gradient rose steeply along the axis of the outer medulla but only slightly along the axis of the inner medulla, whereas the urea gradient rose much more steeply along the axis of the inner medulla. These findings are inconsistent with the hypothesis that active salt transport is the local driving force in the inner medulla, favoring instead an important role for urea. The details of the models of Stephenson and Kokko and Rector are presented in Figure 24. The chloride pump[158] in the thick ascending limb of the loop of Henle, in the outer medulla, is the active source of energy for the whole medulla.[156] The active transport of salt from the lumen of the water- and urea-impermeable thick ascending limb leaves behind a hypotonic fluid rich in urea which flows into the distal convoluted tubule and the cortical and outer medullary collecting ducts; segments which actively reabsorb salt are impermeable to urea but are freely permeable to water (at least the cortical collecting duct) in the presence of AVP or hydropenia. Here, the urea becomes progressively more concentrated in a smaller volume of fluid which enters the inner medullary collecting ducts. As the collecting ducts join they become increasingly permeable to urea, especially in the presence of AVP,[144,146,153,154] allowing the urea to flow along its concentration gradient and approach equilibrium with the adja-

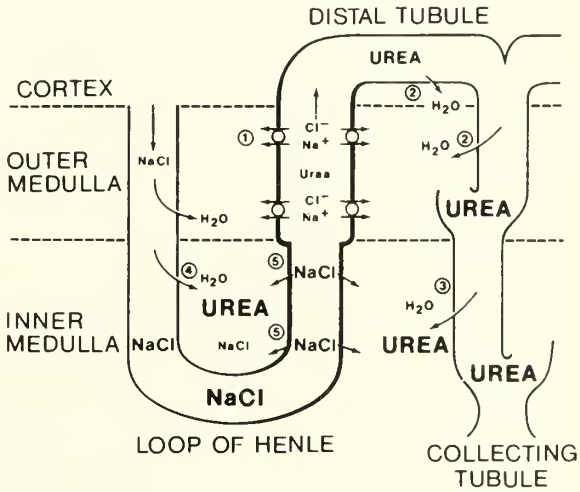

Figure 24.—Recent modification of the countercurrent hypothesis by Stephenson and Kokko and Rector. Both the thin ascending limb in the inner medulla and the thick ascending limb in the outer medulla, as well as the first part of the distal tubule, are impermeable to water, as indicated by the thickened lining in the thick ascending limb. Active chloride (Cl^-) reabsorption, accompanied by passive sodium (Na^+) movement (1), renders the tubule fluid dilute and the other medullary interstitium hyperosmotic. In the last part of the distal tubule and in the collecting tubule in the cortex and outer medulla, water is reabsorbed down its osmotic gradient (2), increasing the concentration of urea that remains behind. In the inner medulla both water and urea are reabsorbed from the collecting duct (3). Some urea reenters the loop of Henle (not shown). This medullary recycling of urea, in addition to trapping of urea by countercurrent exchange in the vasa recta (not shown), causes urea to accumulate in large quantities in the medullary interstitium (indicated by the large type), where it osmotically extracts water from the descending limb (4) and thereby concentrates sodium chloride (NaCl) in descending-limb fluid. When the fluid, rich in sodium chloride, enters the sodium-chloride-permeable (but water-impermeable) thin ascending limb, sodium chloride moves passively down its concentration gradient (5), rendering the tubule fluid relatively hyposmotic to the surrounding interstitium. (Reproduced with permission from Jamison & Maffly.[146(p1060)])

cent interstitium of the inner medulla. The increase in medullary osmolality thus created draws water out of the adjacent tubules, the terminal collecting ducts and especially the descending limb of the loop. The NaCl in this relatively salt-impermeable descending limb becomes progressively more concentrated as the fluid approaches the hairpin turn, while the salt concentration in the adjacent interstitium is somewhat reduced by dilution.

As the luminal fluid with its highest concentration of NaCl rounds the tip of the loop, it enters the water-impermeable, salt-permeable thin ascending limb, and immediately sodium and chloride ions diffuse down their concentration gradient into the surrounding interstitium, thus increasing its osmolality. The luminal fluid left behind becomes relatively hypotonic to the adjacent interstitial fluid (Figures 23 and 24). The rise in osmolality of the latter tends to draw more water into the interstitium from the collecting ducts and tends to dilute the interstitial urea. This process reestablishes the urea gradient from the terminal and inner medullary collecting ducts to interstitium. Urea now diffuses down its gradient from these ducts, thereby increasing the osmolality of the interstitium; more water moves in from the descending limbs and, in so doing, reestablishes the salt gradient and so on. The osmolality of the interstitium continues to rise and water reabsorption from the collecting duct is thus enhanced. Water that has entered the medulla from the descending limb and collecting ducts is carried away by the ascending vasa recta. Quoting from Britton and associates[156]:

> The crux of the matter is that the osmolality of the interstitium depends on the *sum* of the salt and urea contributions whereas the diffusion of salt depends only upon the passive gradient of the ions from thin ascending limbs to interstitium. The model demonstrates how these two gradients are continuously but alternately reformed in an escalating manner as the diffusion of specific solute and water due to one gradient recreates the other. This is an example of the bootstrap concept because the energy of the chloride pump in the cortex and outer medulla is transduced to the high urea concentration in the collecting ducts which primes the solute gradient interaction to increase the osmolality in the interstitium. The situation may be visualized as salt raising its own concentration by hauling on urea's bootstraps and vice versa.

Two recent studies from Jamison's laboratory[159,160] lend added weight to the passive models of Stephenson[151,152] and Kokko and Rector.[144,153] In one study,[159] they examined the contents of the collecting tubule, loop of Henle and vasa recta before and after an infusion of urea to protein-deprived rats and compared the results with similar studies in animals not given urea. Not only did urinary osmolality increase substantially in the urea-infused animals, but water extraction from the descending limb also increased considerably. An additional finding of importance was that the urea concentration in the fluid at the end of the descending limb was appreciably higher than could be explained by simple osmotic flow of water from lumen to interstitium. This strongly suggests that part of the medullary recycling of urea involved its movement from interstitium to urine somewhere in the nephron segment between the end of the proximal tubule and the end of the descending limb. However, Rector[147] has stressed that if a substantial amount of urea is added to the thin descending limb, it will diminish water abstractions from this segment and actually impair the efficiency of the postulated passive model. To the extent that osmotic equilibrium in the thin descending limb occurs by solute entry, the ability of urea to enhance urine concentration will be diminished. The greater the solute urea entry, the lesser the *amount* of water abstracted and the lower the NaCl concentration in the loop fluid delivered to the thin ascending limb.[2] An additional way in which urea may enter the papillary tips and inner medulla was suggested by Gertz and co-workers[161] and confirmed by Schütz and Schnermann.[162] Because the papillary tips are bathed by pelvis urine containing the highest concentration of urea, the latter could diffuse across the pelvis epithelium into the adjacent medulla. Schütz and Schnermann found, in rats, that when the renal pelvis was opened and maintained free of urine, the osmolality of urine emerging from the collecting ducts fell from 1,400 to 800 mOsm per kg. However, if they bathed the exposed papillae in increasingly hypertonic urea solutions, the urinary osmolality rose simultaneously to 2,000 to 2,500 mOsm per kg. Therefore, the pelvis urine appears to be an important source of urea and the absence of this intimate contact between papillae and pelvis urine could impair the function of the countercurrent system.

Rector, in his excellent analysis of the renal-concentrating mechanisms,[144] concluded that not all the available micropuncture studies in rats, hamsters and Psammomys are consistent with the passive model for the production of a maximally concentrated urine, derived primarily from the permeability characteristics of the isolated perfused

rabbit nephron. It may well be that there are important species differences in the intimate mechanism(s) responsible for the optimum function of the renal medullary countercurrent system.

In the other study from Jamison's laboratory,[160] the differences in sodium concentration between fluid in the thin limb of Henle and that in adjacent vasa recta plasma in normal hydropenic rats were examined. Assuming that the vasa recta plasma was an accurate indicator of the sodium concentration in the interstitial fluid, they found a clear-cut gradient favoring passive reabsorption or diffusion of sodium. The results of both of these studies fulfill key requirements of the passive models.

The anatomic arrangement of the vasa recta and their function as a countercurrent exchanger greatly facilitates the function of the loop in the maintenance of the hypertonic interstitium (Figures 22, 23 and 25) and, at the same time, allows water from the descending limb and collecting duct to be removed from the medulla by way of the ascending vasa recta. The endothelium of the vasa recta is freely permeable to water, much less permeable to plasma proteins, and its permeability to smaller solutes, such as electrolytes, lies between these extremes.

As blood in the vasa recta descends in the capillary loop, it approaches osmotic equilibrium with the surrounding hypertonic environment by the passive diffusion of sodium salts and other solutes, notably urea, *into* the capillary lumen while water diffuses out along its osmotic and hydrostatic pressure gradient. The rapidity of blood flow creates an osmotic disequilibrium in which the osmotic pressure of the interstitial fluid and the hydrostatic pressure in the capillary together oppose the oncotic pressure exerted by the plasma proteins. This generates the net force. As the blood doubles back on itself and flows toward the corticomedullary junction in the ascending vasa recta, urea and sodium salts return to the interstitium while water diffuses into the blood. In the ascending limb plasma, the concentration of the small solutes now exceeds that in the adjacent interstitium and this osmotic force, plus the now additive oncotic pressure of the proteins, cause a net fluid entry into the blood. The quantity of water entering exceeds that lost from the descending vasa recta and is equal to the volume of fluid reabsorbed from the collecting tubule and descending limb of the loop of Henle. The net effect is the free diffusion of salt and urea from ascending to descending, and of water from descending to ascending limb of the vascular loop, and return to the bloodstream of the water that has diffused into the medulla from the descending limb of the loop of Henle and the collecting ducts. Therefore, the vascular loop, as a countercurrent exchanger, minimizes the loss of excess sodium

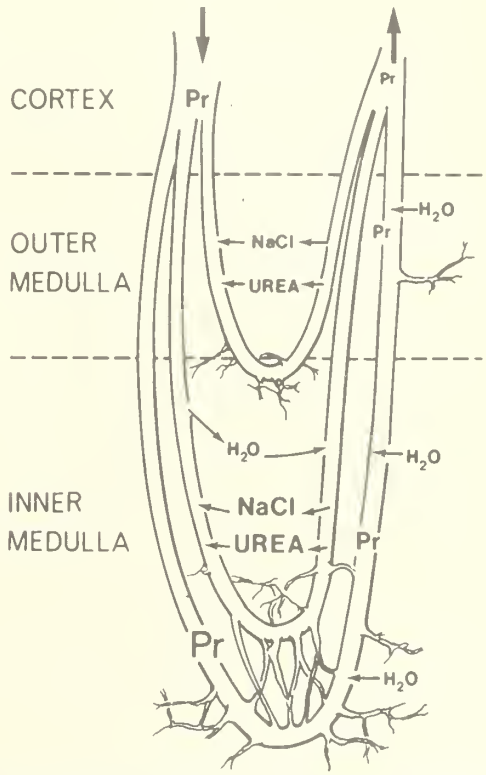

Figure 25.—Countercurrent exchange by the vasa recta. The medullary circulation, unlike the loops of Henle, consists of a network of channels with main thoroughfares (the vasa recta) and branch connections. Pr denotes plasma protein. The size of type indicates the relative concentrations of each solute with respect to its location in the medulla but not necessarily with respect to other solutes. The progressive rise in the concentration of sodium chloride (NaCl) and urea in the medullary interstitium is due to the loop of Henle and collecting tubule. Because the capillaries are permeable to sodium chloride and urea, these solutes enter descending vasa recta and leave ascending vasa recta. This transcapillary exchange helps trap the solutes in the medulla. Conversely, water leaves the descending vasa recta, causing the plasma protein concentration to increase. In the ascending vasa recta the sum of oncotic (that due to plasma protein) and osmotic (that due to nonprotein solutes) pressures results in capillary fluid uptake. Thus, water reabsorbed from the collecting tubule and the descending limb of Henle is removed from the medulla and returned to the general circulation. The vasa recta function in a dual capacity—trapping solute and removing water—in order to preserve the hyperosmolality of the renal medulla. (Reproduced with permission from Jamison & Maffly.[146(p1064)])

and urea from the medulla and maintains the hypertonic gradient which would be dissipated if the vasa recta blood did not double back on itself (Figures 22, 23 and 25).

The "trapping" and recycling of urea in the medulla creates the surprising phenomenon in which the net resorption of urea into the bloodstream (normally 40 percent to 50 percent of the filtered urea) occurs only in the cortical parts of the nephron. The urea which is resorbed from the collecting ducts, and which approaches the same concentration in medullary water and collecting-duct fluid, is trapped in the medullary interstitium from which an amount approximating proximal resorption diffuses into the loop (? descending limb) of Henle (Figures 23 and 25). As urea, during antidiuresis, approaches diffusion equilibrium across the collecting duct (equal concentration in medullary water and collecting-duct fluid), it contributes equally to the total osmolality of the medulla and urine. Therefore, it increases the osmotic pressure of the urine beyond that attained by the osmotic equilibrium of collecting-duct fluid with the hypertonic NaCl in the interstitium.

In summary, the hypertonicity in the medulla and the magnitude of the hypertonic gradient from corticomedullary junction to papilla at any given moment during both diuresis and antidiuresis will be directly proportional to the number and length of the loops of Henle, the rate of salt delivered to and actively transported across the ascending limb and the load of urea presented to the collecting duct; they will be inversely proportional to the velocity of medullary blood flow, the flow of tubular fluid in the loop of Henle and the rate of water transport into the medulla from the collecting ducts and descending limb of the loop.

Role of AVP and the Control of Urine Concentration and Dilution

Although solutes are actively resorbed in the distal part of the distal convoluted tubule and the cortical segment of the collecting duct, the resorption of water in these segments is dependent primarily on the presence of AVP (Figure 23). In the absence of AVP, there is a minimal transport of water into the surrounding capillary beds, and the dilute fluid from the ascending limb and the more proximal segment of the distal convoluted tubule is made progressively more hypotonic by continued active solute resorption. Therefore, when AVP is absent, the fluid in the distal portion of the cortical collecting duct approaches the lowest osmolality observed throughout the nephron, possibly between 15 and 20 mOsm per liter. This is the situation seen during maximal sustained water diuresis, in diabetes insipidus (DI) or in any physiologic state that prevents AVP from acting on this segment of the nephron. Although the medullary collecting ducts are also relatively impermeable to water in the absence of AVP, the pronounced gradient between the hypotonic luminal fluid and hypertonic interstitium allows some back diffusion of water, the magnitude of which is determined by the volume per minute delivered to the collecting duct during water diuresis. If this volume is small enough, a moderately hypertonic urine can be formed in the absence of AVP.[163]

When a maximal amount of AVP is available, the cortical collecting duct is freely permeable to water and, as the solutes are actively resorbed, the tubular fluid in this segment will approach isotonicity. If less than maximal amounts of AVP are available, the permeability of this segment will be proportionately decreased, lesser amounts of water will back diffuse with the solute, and the tubular fluid will not reach isotonicity. Therefore, AVP simply permits the back diffusion of water to occur along established concentration gradients. Because approximately 90 percent of the solute delivered into the distal convoluted tubule and cortical collecting duct is resorbed, at least 90 percent of the water delivered to it will back diffuse. It is apparent that a reduction in the resorption of solutes in these segments, such as may occur during an osmotic diuresis, will increase the volume of residual isosmotic tubular fluid delivered into the medullary collecting tubules during the maximal AVP activity. As a consequence of the alterations taking place in the thick ascending limb, distal convoluted tubule and cortical collecting duct, the fluid delivered into the medullary collecting duct may be of minimal osmolality and approximately the same volume as that delivered into the distal convoluted tubules, or the luminal fluid may decrease to the smallest volume necessary to excrete the remaining urinary solutes in isotonic or isosmotic concentration.

The isotonic fluid entering the medullary collecting duct courses down through the hypertonic medulla. In the hydropenic animal (maximal AVP activity), this small volume of fluid is maximally concentrated by the back diffusion of water along

its osmotic gradient into the hypertonic interstitium. The maximal concentration of urine that is usually achieved in the moderately hydropenic human is approximately 1,000 to 1,100 mOsm per liter. However, in circumstances of a prolonged water deficit, such as may occur during complete abstinence from water for 72 hours, the urinary concentration may attain values of 1,300 to 1,400 mOsm per liter. As stated earlier, the attainment of these maximal values is not due to a further increase in circulating AVP or in the permeability of the collecting duct but, rather, to the continued decrease in medullary blood flow and increase in medullary tonicity.

The volume abstracted in the final concentrating process is ordinarily quite small, being below 1.5 ml per minute. This water is returned to the circulation via the vasa recta.

The exact cellular mechanism(s) by which AVP creates a physicochemical change in certain epithelial membranes to allows the differential passage of water, urea and salt is still unknown. However, the recent reviews by Andreoli and Schafer[145,164] and Hays[165] have added greatly to our understanding.

It is of great interest that in mammalian cortical medullary collecting ducts AVP enhances the transcellular movement of water without any effect on urea or sodium transport.[145,164] This is in contrast to its effect on amphibian skin and bladder where water, urea and sodium permeate the hormone-responsive apical membranes through what appear to be parallel but dissociated routes.[145,164] In fact, there may even be separate membrane-bound adenyl cyclases controlling the hormone's stimulation of water and sodium transport.

In both species, the initial step in the action of AVP is its binding to receptors in the basal lateral membrane of the responsive cells. As mentioned earlier, this receptor-hormone interaction may not only initiate the cellular processes responsible for water and solute transport, but its magnitude and saturation may also determine the metabolic turnover and degradation of the hormone. Exactly how the spatial configuration and physicochemical structure of AVP determine its binding to the receptor is beyond the scope of this chapter, but an in-depth analysis of the available information can be found in the review of Walter and associates.[166]

Once AVP is bound to its receptor on the basal (peritubular) surface of the cell, it initiates a series of reactions which lead to the increased apical (luminal) permeability to water and en-

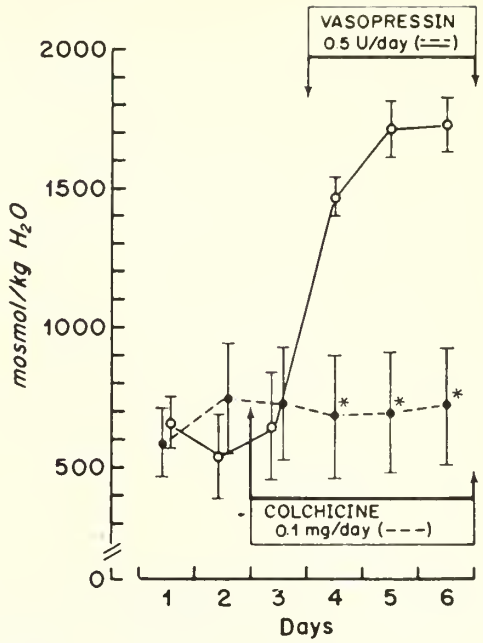

Figure 26.—Response of urine osmolality to vasopressin in control rats (o—o) and in rats treated with colchicine on three to six experimental days (------). Each group consisted of six animals. Asterisks indicate values significantly differen(from controls ($P<0.05$ in t test). (Reproduced with permission from Douzsa and Barnes.[171])

hanced transcellular hydraulic flow along osmotic gradients. First in this series is the activation of the membrane-bound adenyl cyclase. The latter stimulates the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (3′5′-cAMP), the intracellular concentration of which is regulated by phosphodiesterase. The more active or the greater the amount of the latter, the greater the inactivation and breakdown of cAMP. These initial steps, proposed by Handler and Orloff[167] to be fundamental to the action of AVP, have been widely confirmed and accepted.

The subsequent intracellular steps are actively being investigated, and have been discussed in detail by Dousa and Valtin[168] and Andreoli and Schafer.[169] Based on the current concepts of the intracellular role of cAMP in various tissues,[169] it appears that cAMP, in turn, activates one or more protein kinases in the cell, thus regulating the level of phosphorylation of specific cell proteins which may be bound or involved in the intracellular formation, aggregation and translocation of certain unique intracellular organelles. These organelles are known as microtubules and microfilaments, the formation of which accompanies and may be essential for the hydro-osmotic

effect of AVP.[170] Whatever the role of microtubules and microfilaments in the action of AVP, it is clear that acute and chronic administration of colchicine (the classic antimitotic agent) and the related plant alkaloid vinblastine can substantially impair the hormone's hydro-osmotic effect on mammalian collecting ducts (Figure 26) without themselves altering glomerular filtration rate (GFR), solute excretion or urine flow. Furthermore, this inhibitory effect did not involve an action of these alkaloids on the activity of the enzymes involved in cAMP metabolism and cAMP-dependent phosphorylation.[171] It is well established that these antimitotic agents interfere with intracellular microtubule assembly *in vitro* and exert disruptive effects on cytoplasmic microtubules *in vivo*.[170]

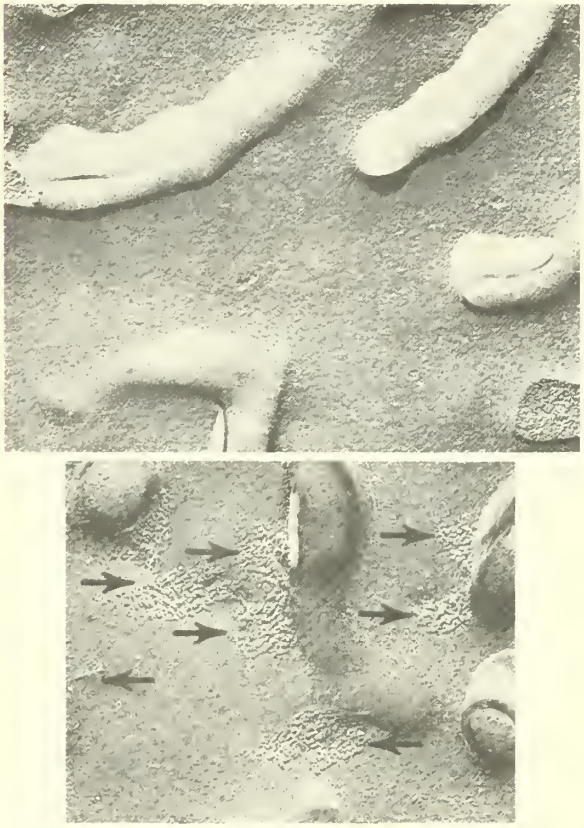

Figure 27.—Above, Fracture face of the luminal membrane of a granular cell from toad urinary bladder not stimulated with vasopressin. Ridgelike microvilli are prominent and intramembranous particles are distributed randomly over the entire membrane face (reduced from ×47,500). **Below**, Fracture face of granular cell membrane from toad bladder stimulated with vasopressin (20 mU per ml) in the absence of an osmotic gradient. Aggregates **(arrows)** appear identical to those found after vasopressin stimulation in the presence of an osmotic gradient (reduced from ×60,000). (Reproduced with permission from Kachadorian et al.[173])

Numerous morphologic studies have shown a temporal and spatial relationship between the presence of microtubules or microfilaments, or both, and a variety of cell processes involving the movement of cellular components (such as pigment granules), phagocytosis, release of secretions, mobility of membrane receptors, pinocytosis and exocytosis.[170] How this tubular aggregation and assembly can be related to water transport across AVP-responsive epithelium is unknown. As suggested by Taylor,[170] it is possible that it may be related to the dramatic structural or organizational change in the (epithelial cell) luminal membrances of amphibian bladders in response to AVP as described recently by Kachadorian and associates.[172,173] By using freeze-fracture electron microscopy, they were able to consistently show that in the presence or absence of an osmotic gradient vasopressin and dibutyryl, cAMP induced a reversible organized aggregation of intramembranous particles (presumably representing intramembranous proteins) in epithelial cell luminal membranes (see Figure 27). Taylor speculated that microtubules and microfilaments may play a role in determining the distribution of intramembranous particles in the amphibian bladder. These organelles may play an anchorage role or may be the effectors of movement of intramembranous particles in the plane of the plasma membrane, thereby controlling the surface topography of the luminal membrane and, in turn, its permeability characteristics.

In summary, AVP binds to high-affinity receptors on the basolateral or contraluminal surface of responsive epithelial cells which results in an adenyl cyclase-mediated generation of cAMP from ATP. The cAMP, in turn, mediates the kinetics of apical or luminal membrane-bound protein phosphorylation-dephosphorylation reactions which somehow interact with the formation and assembly of the microtubules. These permeability steps are associated with or followed by the permeability change(s) in the luminal membrane which cause increased hydro-osmotic flow of water, antidiuresis and a more concentrated urine. The luminal surfaces of the cortical and medullary collecting ducts constitute the rate-limiting site for water transport and the final locus of action of AVP-mediated effects on transepithelial water permeation.[145]

Schafer and Andreoli[145,164] recently reviewed in depth various studies contributing to an understanding of the physicochemical factors involved

in the hormone-regulated movement of water across the luminal membrane, such as the way in which water traverses this hormone-regulated membrane. A brief summary of their conclusions is presented and the reader is referred to their excellent analysis for additional information. (1) Water probably traverses the luminal membrane through hydrophilic sites having the characteristics of narrow aqueous channels (effective radius 1.8 to 2.0 A) and AVP increases water permeability by increasing the number of such hydrophilic sites ("pores") in these membranes rather than increasing pore radii. (2) The primary process for hormone-dependent water movement is diffusion rather than laminar net volume; that is, bulk flow through aqueous channels, pores or cylinders as originally proposed by Koefoed-Johnsen and Ussing.[174] (3) The experimental observation that AVP enhances not only the diffusion of water but also certain small lipophilic (high oil/water partition ratios) molecules such as butyramide, isobutyramide and antipyrine across the isolated, perfused cortical collecting duct of the rabbit is best explained by assuming parallel diffusion pathways influenced by the hormone. (4) The water permeation pathways virtually exclude the diffusion of small hydrophilic molecules such as urea and thiourea as well as the electrolytes sodium and chloride.

Under normal physiologic conditions, the maximal urinary osmolality is determined by the magnitude of the hypertonicity of the medullary interstitial fluid bathing the collecting tubules and by their permeability to water. The available data suggest that in certain circumstances the concentrating process is limited by a maximal rate at which free water can be abstracted from the tubular urine. Because the volume of the water resorbed ordinarily may exceed considerably the volume delivered to the collecting tubule, it is obvious that the maximal rate of back diffusion of free water can be measured only when a large volume of isotonic fluid is delivered to this segment in the hydropenic animal. This can be achieved by the administration of an osmotic diuretic.

Figure 28 illustrates the effects of increasing solute excretion on maximal urinary osmolality in the hydropenic human being administered a continuous infusion of vasopressin. It is readily apparent that as the solute load increases, the maximum concentration of the urine falls in an asymptotic fashion toward the plasma osmolality

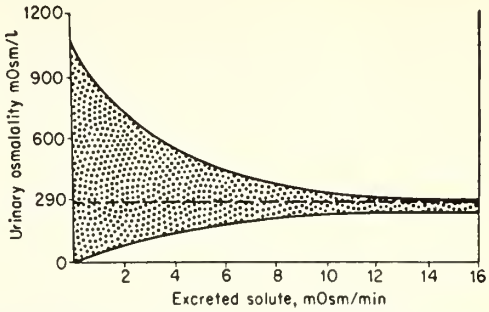

Figure 28.—The effect of a progressive increase in solute excretion on the maximal urinary osmolality in the hydropenic animal (above horizontal line which represents plasma osmolality) and minimal urinary osmolality during water diuresis (below horizontal line). (Reproduced with permission from Kleeman & Vorherr.[143(p1483)])

(285 mOsm per liter). Under these circumstances, increasing amounts of isosmotic fluid are delivered to the concentrating segment of the nephron, and it can be calculated that the maximal amounts of water abstracted from these relatively large volumes as they pass through the collecting tubule approach 5 to 8 ml per minute. This rate may be altered by many factors, including, of course, renal functional mass.

Minimal osmolality and maximal volume of the urine during a water diuresis (absence of AVP) may also be influenced by the rate of solute excretion. Figure 28 illustrates that as solute excretion is increased during a maximal diuresis, the osmolality of the urine increases in an asymptotic manner toward isotonicity. These alterations would, of course, be the result of the decreased fractional solute resorption in the diluting segment of the nephron (thick ascending limb and distal convoluted tubule). The residual urine leaving this segment during maximal water diuresis would approach isotonicity as proportionately less and less of the solute delivered to it is reabsorbed.

If the back diffusion of free water in the cortical and medullary collecting tubule is a passive process, what are the factors limiting its maximal rate? During osmotic diuresis the back diffusion of increasing quantities of water into the hypertonic interstitium would, of course, reduce the hypertonicity of the interstitium, and this, in turn, would decrease the maximal concentration of the urine if the interstitial fluid and urine are in osmotic equilibrium. The model earlier described for the production of maximal medullary hypertonicity requires that urea be progressively con-

centrated in the distal convoluted tubule and collecting duct and, therefore, in medullary interstitium, and, in turn, that sodium chloride be maximally concentrated by water abstraction in the descending limb of the loop of Henle. As progressively more water is obligated or held back in the lumen during an increasing osmotic diuresis, it would progressively lower tubular urea concentration in the distal nephron and NaCl concentration in the descending limb, further reducing the medullary interstitial concentration of those solutes responsible for its hypertonicity. Also of importance in limiting the final back diffusion of free water is the fact that the volume and velocity of flow of the fluid passing down the medullary collecting duct progressively increase during osmotic diuresis, leaving less and less time for contact between the tubular urine and the cells of the collecting tubule. It also should be pointed out that efficiency of any countercurrent multiplier (including the loop of Henle) mechanism is inversely related to the velocity of flow. Osmotic diuretics may also reduce the hypertonicity of the renal medulla by increasing medullary blood flow which, in turn, decreases the "trapping" efficiency of the countercurrent exchange function of the medullary circulation. Therefore, during an osmotic diuresis maximal hypertonicity of the medullary interstitium cannot be achieved because of the decreased efficiency of the countercurrent exchange and multiplier mechanisms. This would contribute materially to limiting the maximal rate of free water resorption and urinary concentration during osmotic diuresis.

TABLE 7.—*Sequence of Events in Water Diuresis*

- Ingestion of water load (1,000 to 1,500 ml)
- Dilution of all body fluids, hydration of cells of supraoptic nuclei, inhibition of secretions of antidiuretic hormone (arginine vasopressin) from the neurohypophysis
- Destruction of circulating arginine vasopressin (half-life approximately 9 to 16 minutes) requires 60 to 90 minutes to reach peak water diuresis
- No action of arginine vasopressin in distal nephron (cortical and medullary collecting ducts) permits maximal impermeability of these segments to water so that almost all water delivered to them appears in the urine (approximately 10 percent to 15 percent of the filtered water)
- Continued normal resorption of salts; therefore, urine of minimal solute concentration and maximal volume

TABLE 8.—*Sequence of Events in Maximal Antidiuresis*

- Moderate negative water balance, such as rigid water restriction for 24 hours
- Negative water balance of approximately 1,500 ml or 1 percent to 2 percent of body weight
- Hyperosmolality of all body cells with dehydration of cells of the supraoptic nuclei
- Release of impulses down neurohypophyseal stalk to posterior pituitary gland; release of arginine vasopressin (AVP) into circulation on sustained basis
- AVP acts on cortical and medullary collecting duct to make these segments freely permeable to water and the latter flows along concentration gradients established by continued solute resorption
- Approximately 80 percent to 90 percent of solute reaching distal convoluting tubule is actively resorbed here; 80 percent to over 90 percent of water is resorbed, leaving small volumes of isotonic fluid to be delivered into medullary collecting duct
- In collecting duct water continues to passively back diffuse into hypertonic interstitial tissue of medulla until urine and medulla reach maximal and equal concentrations; small volume reaching collecting duct is reduced from a third to a fourth of its volume and is maximally concentrated (1,100 to 1,300 mOsm per liter; specific gravity, 1.037)

It is apparent then that active reabsorption of water need not be invoked to explain its movement anywhere in the nephron. Water diffuses passively along osmotic gradients, its movement being limited only by the magnitude of the gradient and the relative permeability of various segments of the nephron.

Therefore, the maximal urine to plasma (U/P) concentration ratios during oliguria and the maximal rate of back diffusion of free water during osmotic diuresis, although of considerable physiologic importance in the homeostatic regulation of water, do not denote any form of tubular maxima limited by an active transport process.

Although the collecting tubule is relatively impermeable to water in the absence of arginine vasopressin, if the volume of fluid delivered to this segment is small enough, a moderately hypertonic urine can be produced. This phenomenon is most strikingly seen in the production of a substantially hypertonic urine during hydropenia in rats with congenital diabetes inspidus.[175,176]

Tables 7 and 8 summarize the physiologic events responsible for a maximal water diuresis and antidiuresis after an acute water load or period of hydropenia.

Concept of Free Water Clearance

For functional purposes, Homer Smith and his associates conceived of urinary water as being divided into two moieties: that volume necessary to excrete all urinary solutes in isosmotic proportion, and that volume resorbed from the urine without solute during the concentrating process or "freed" of solute during the diluting process.

TABLE 9.—*Physiologic Factors Altering Maximal Renal Concentrating Capacity (in Presence of Maximal Arginine Vasopressin)*

Rate of solute excretion or osmotic diuresis (such as sodium chloride, urea, glucose, mannitol)
Glomerular filtration rate
Rate of medullary blood flow
Protein content of the diet
Water intake and the state of hydration
Salt (NaCl) intake and salt depletion
Presence or absence of an adequate amount of adrenal glucocorticoid and mineralocorticoid
Altered renal medullary prostaglandin synthesis by interstitial cells of the renal medulla
Diuretics with the exception of aminophylline

Homer Smith called these two moieties of urinary water Cosm (osmolar clearance) and C_{H_2O} (free water clearance), respectively.

As mentioned, the osmolar clearance represents the volume of urine necessary to excrete all the urinary solutes in an isosmotic solution. This would include the solutes remaining after all proximal and distal nephron segments had acted upon them. It is calculated as follows:

$$\text{Cosm} = \frac{\text{Uosm V}}{\text{Posm}}$$

Uosm = urinary osmolality (mOsm per liter)
V = urinary flow (ml per minute)
Posm = plasma osmolality (mOsm per liter)
Uosm V = solute excretion (mOsm per minute)

When Uosm is hypertonic to plasma, the ratio Uosm/Posm will exceed 1. Therefore, (Uosm/Posm) × V will exceed urinary volume, or Cosm will exceed urinary volume. Thus:

$$V = \text{Cosm} + C_{H_2O}$$
$$C_{H_2O} = V - \text{Cosm}$$

Therefore, the free water clearance will have a negative value when the urine is hypertonic and a positive value when the urine is hypotonic. Expressed another way, free water clearance is that quantity of water excreted which is virtually freed of solutes during the process of urinary dilution.

An example of the calculation of osmolar clearance and positive and negative free water clearance will assist in clarifying these terms. Assume that 100 ml of glomerular filtrate is being formed per minute and that 80 percent of this filtrate is resorbed in isosmotic proportions by the beginning of the descending limb of the loop of Henle. In the descending limb, an additional 5 ml of water is reabsorbed. Assuming that no water is resorbed in the ascending limb, 15 ml of hypotonic (150 mOsm per liter) fluid is delivered into the distal convoluted tubule. If during maximal AVP activity 90 percent of the remaining solutes were resorbed and enough water back diffused to bring the urine to isotonicity by the end of the cortical collecting duct, 1.5 ml of isotonic fluid would be delivered to the medullary collecting duct. Here, fluid would be withdrawn until 0.3 ml maximally concentrated urine of 1,400 mOsm per liter was formed. If we assume plasma osmolality to be 285 mOsm per liter, then

$$\frac{1{,}400 \times 0.3}{285} = \frac{420}{285} = 1.5 \text{ ml per minute} = \text{Cosm}$$
$$V - \text{Cosm} = C_{H_2O}$$
$$0.3 - 1.5 = -1.2 \text{ ml per minute}$$

The magnitude of the negative free water clearance, or the fluid back diffusing in the ultimate concentrating process, equals 1.2 ml per minute.

Conversely, if 15 ml of hypotonic fluid were delivered into the distal tubule in the absence of AVP and 90 percent of the solute were reabsorbed without water, approximately 15 ml of a dilute fluid (osmolality of 28.5 mOsm per liter) would be delivered into the final segment. Here, a minimal amount of fluid would be removed in the absence of AVP (2 ml per minute), leaving 14 ml of urine with a final concentration of 30 mOsm per liter.

$$C_{H_2O} = V - \text{Cosm}$$
$$\text{Cosm} = \frac{14 \times 30}{285} = 1.5 \text{ ml per minute}$$
$$C_{H_2O} = 14 - 1.5 = 12.5 \text{ ml per minute}$$

In recent years, the generation of a positive C_{H_2O} during a maximally sustained water diuresis in dogs and humans has been used as an index of NaCl reabsorption in the diluting segment of the nephron.[177] Maximal urine volume (V), under these conditions, has been used as an index of NaCl delivery to this site(s). The exact anatomic location of this segment is not actually designated. In the state of physiologic diabetes insipidus (no apparent circulating AVP), it includes at least the thick ascending limb, the distal convoluted tubule, the cortical collecting duct, and some have even included the medullary collecting duct. To use C_{H_2O} and V in this manner as an approximation of distal nephron NaCl reabsorption, one must assume little or no back diffusion of water in this segment. It is clear from the micropuncture study of Jamison and colleagues[178] in rats with hereditary diabetes insipidus that even in the absence of AVP at least 2 percent of the filtered load of water is reabsorbed in the medullary collecting duct.

In Table 9 are listed the physiologic factors

altering the maximal renal-concentrating capacity during hydropenia or when there is a maximal effect of AVP on the kidney.

Solute Excretion Rate

The effect of the rate of solute excretion, or osmotic diuresis has been described above.

Glomerular Filtration Rate

When the glomerular filtration rate (GFR) is functionally decreased by more than 25 percent, insufficient NaCl and urea are delivered to the ascending limb and collecting duct, respectively, to provide maximal interstitial hypertonicity and, therefore, maximal urinary concentration. However, a decrease in GFR of less than 25 percent has been shown to enhance slightly the maximal urinary osmolality of the hydropenic animal.

Medullary Blood Flow Rate

The effect of change in medullary blood flow has been discussed earlier. However, it may be emphasized that if other factors remain relatively constant, a decrease in medullary blood flow increases maximal urinary concentration; an increase in medullary blood flow will decrease the maximal osmolality.

Dietary Protein

An increase in the protein content of the diet increases the maximal capacity of the concentrating mechanism. Although it is possible that a low-protein diet may impair slightly the ability of the kidney to concentrate nonureal urinary solutes, the primary effect of protein on the concentrating mechanism is due rather to the resultant variations in urea excretion. It has been shown that increased urea excretion enhances the concentrating mechanism.[144,146] From micropuncture studies and analysis of the medullary tissues of hydropenic animals, it is evident that urea exists in equal and high concentration in the urine, in the tip of the vascular loop and in the interstitium of the surrounding medulla.[144,146] Thus, in the hydropenic animal under the maximal influence of AVP, urea appears able to be diffused freely across the cells of the collecting tubule; as water is resorbed in this segment, urea follows it passively along its own concentration gradient. This, of course, adds to the hypertonicity of the interstitium and enhances the maximum concentrating ability of the nephron. The protein content of the urea formed from the diet does not appear to alter the maximal diluting capacity except by its effect on total solute excretion. The greater the protein content of the diet, therefore, the greater would be the back diffusion of urea during the concentrating process, and the more hypertonic the medullary interstitium.

Hydration

Prolonged overhydration impairs the concentrating mechanism, whereas chronic dehydration enhances it.[179] This effect of chronic overhydration may be of clinical significance, particularly in patients with psychogenic polydipsia. A mild concentrating defect may be evident after a few days of cnronic overhydration. However, polydipsia of months or years' duration may impair the concentrating mechanism substantially. These persons may be unable to form urine with a concentration greater than isotonicity. The observation of this concentrating defect may lead to the mistaken diagnosis of polyuria and polydipsia secondary to a primary renal tubular lesion. Rigid water restriction for several days in these patients, although difficult to maintain, will definitely enhance the maximal concentrating capacity. These persons are capable of producing a normal maximal water diuresis, and their kidneys can respond to the administration of AVP with the production of an isotonic or only slightly hypertonic urine. There is evidence that this concentrating defect is due to a reduction in medullary hypertonicity rather than any decrease in tubular responsiveness to AVP.[180] The prolonged water ingestion in some way diminishes the efficiency of the countercurrent exchange and multiplier mechanisms. The augmentation in concentrating capacity associated with prolonged water restriction, conversely, is associated with an increase in medullary tonicity. The impaired responsiveness to AVP and the production of an increasingly concentrated urine in congenital diabetes insipidus rats during water restriction is a most striking example of this phenomenon.

Sodium Chloride Balance

It is readily apparent from the discussion of the function of the loop of Henle and the production of a hypertonic interstitium that if the active reabsorption of chloride accompanied by passive reabsorption of sodium in the thick ascending limb is defective or altered, or if the amount of sodium chloride delivered to this site is diminished, the critical force for initiating a hypertonic medullary interstitium will be inadequate, the

"bootstrap" effect mentioned earlier will be blunted, water will not adequately diffuse out of the descending limb, and the build-up of the NaCl concentration in the loop and ascending thin limb essential for the passive step of the countercurrent multiplier will not occur. Thus, for pathologic or physiologic reasons, we are left with a less hypertonic inner medulla and an inability to form a maximally concentrated urine in the terminal collecting ducts. It is often observed clinically that patients who are severely salt depleted may, in spite of their pronounced oliguria, continue to produce an isotonic or only slightly hypertonic urine. This phenomenon may be secondary to a reduced sodium content of the interstitial tissues of the medulla.

Adrenal Corticoids

Both glucocorticoid (cortisol) and mineralocorticoid (aldosterone) seem necessary for the production of a maximally concentrated urine during hydropenia.[181] A distinct concentrating defect has been repeatedly observed in patients with adrenal insufficiency. This defect is probably due to a decrease in the delivery of NaCl to the loop of Henle and impaired active resorption of NaCl in the ascending limb of the loop. The possibility that glucorcorticoids, through their permissive role, are essential for the normal action of AVP on the nephron has not been ruled out as a factor contributing to the concentrating defect of adrenal insufficiency. Recent studies suggest that glucocorticoids may enhance the hydroosmotic effect of AVP on the epithelial membranes by inhibiting the generation of prostaglandins.[182]

Prostaglandins

Secretion of prostaglandin E (PGE) by the interstitial cells of the renal medulla or the cells of the medullary collecting duct clearly modulates the action of AVP on mammalian nephrons.[183-185] A local increase in PGE concentration inhibits the action of AVP (decreases maximal urinary concentration) while a decrease in PGE enhances the antidiuretic effect of AVP.[184,185] This modulating capacity of PGE appears to be exerted through its ability to alter the AVP activation of adenyl cyclase. For example, the concentrating defect caused by potassium depletion is associated with an increased renal medullary generation of PGE and the defect can be ameliorated substantially by the inhibition of PGE synthesis in dogs.[186] These observations on the AVP-PGE interrelationship indicate that any physiologic or pathophysiologic change which alters the renal response to AVP must engender the possibility that the deviation from normal is caused by a change in the synthesis of PGE. It is also of great interest that recent studies have shown that vasopressin can increase renal PGE biosynthesis in rabbits, normal rats and the strain of Brattleboro rat.[183]

Diuretics

Diuretic agents (such as ethacrynic acid, furosemide and mercurials) impair maximal concentrating capacity by inhibiting active chloride resorption in the thick ascending limb of the loop of Henle and by producing chronic potassium depletion.[187] It is of great interest that the xanthine diuretic aminophylline actually enhances both maximal diluting and maximal concentrating capacity of mammalian nephrons.[188] It seems to act by increasing the delivery of sodium and water to the loop of Henle and distal nephron without interfering with NaCl resorption in any segment other than the proximal tubule. It is obvious that the concentrating capacity of the kidney cannot be evaluated while the patient is receiving a "loop" diuretic.

Pathologic Factors Altering Maximal Concentrating Capacity

All the clinical syndromes listed in Table 10 impair the kidney's ability to form a concentrated, or maximally concentrated, urine by producing singly or in combination the following lesions: (1) A progressive destruction of renal mass, leaving a reduced number of functional nephrons, which would cause an increased GFR or increased osmotic (primarily urea and NaCl) load per nephron, or both. The ensuing osmotic diuresis in each tubule could reach enormous proportions, thus causing the same "defect" in concentrating capacity that we see during an osmotic diuresis in normal animals and humans (Figure 28), and for the same reasons. (2) Organic lesions of the renal medulla that disrupt the anatomic arrangement of the loop of Henle and the vasa recta or produce a specific defect in the active transport capacity of the thick ascending limb of the loop, which would seriously interfere with the countercurrent exchange and multiplier functions of this part of the kidney. The maximal osmolality of the urine would be equal to or less than the reduced hyperosmolality of the medullary (or papillary) interstitium. (3) Organic lesions in the cortical

TABLE 10.—*Clinical States That Impair Maximal Renal Concentrating Capacity*

Chronic renal failure (pyelonephritis, glomerulonephritis, nephrosclerosis, gout, polycystic and medullary cystic kidneys, analgesic nephropathy and other causes of interstitial nephritis
Diuretic phase of acute tubular necrosis of any etiology
Hypokalemic nephropathy
Hypercalcemic nephropathy
Hyperaldosteronism (primary)
Multiple myeloma, amyloid disease and the Sjögren syndrome
Postobstructive uropathy
Postrenal transplantation
Sickle-cell anemia
Congenital nephrogenic diabetes insipidus (failure to respond to antidiuretic hormone)
Chronic ingestion of high doses of lithium
Methoxyflurane anesthesia
Psychogenic polydipsia
Chronic glucocorticoid and mineralocorticoid deficiency (Addison disease)
Dichlormethyltetracycline (Declomycin)

or medullary collecting ducts, or both, which would impair their response to AVP. Such lesions would cause a polyuric syndrome associated with the persistence of a *hypotonic* urine despite hydropenia with high circulating levels of AVP or the administration of vasopressin (Pitressin).

Diabetes Insipidus

Diabetes insipidus (DI) is a syndrome that results from failure of the neurohypophyseal system to produce or to release a quantity of AVP sufficient to bring about the normal homeostatic renal conservation of free water. In recent years this disorder has been called vasopressin-sensitive DI to distinguish it from the rare congenital and familial disorder nephrogenic diabetes insipidus (NDI), in which greater than normal amounts of AVP are produced; the latter has no observable effect on the diluting segments of the nephron. It is obvious that the disturbance in water metabolism would be identical in both states, each characterized by the continuous production of an inappropriately large volume of hypotonic urine (specific gravity usually less than 1.005 and osmolality less than 200 mOsm per liter). Diabetes insipidus may be complete or partial, permanent or temporary.

This syndrome has been produced experimentally in many mammals over several decades. In general, to produce a persistent abnormality in the production or release of AVP, it has been necessary to destroy either the supraoptic nuclei or a major part of the neurohypophyseal tract or pituitary stalk. The simple removal of the posterior lobe, although at times associated with a short period of DI, has never been capable of producing the sustained disorder. This is strong evidence in favor of the currently accepted view that the neural lobe, although the major site for storage and release of the hormone, is not involved in its synthesis, and that in the absence of the posterior pituitary the newly formed hormone can still be released into the circulation.

Pathophysiology

All the clinicopathologic lesions associated with DI involve the supraoptic and paraventricular nuclear areas or a major portion of the stalk.

It is generally concluded today that a primary functional abnormality in the thirst mechanism is not an important factor in the polydipsia, but that the latter is a response to the profound renal water loss. However, it is not inconceivable that the associated hypothalamic lesions might at times produce a specific disorder of the thirst mechanism. In fact, the authors have had the opportunity of observing a patient with well-documented DI who, on recovery from this illness, was left with a severe thirst in spite of the fact that his renal-conserving mechanism for water was normal. Over the period of a year there was a gradual reduction in the thirst of this patient, and he was able to do well with increasingly smaller oral intakes of water. This may be a conditioning defect of the thirst center, secondary to the excessive water ingestion of DI.

After experimental injury to the neurohypophyseal system, the development of the DI syndrome frequently follows a characteristic triphasic pattern (Figure 29). This pattern, which may also occur clinically after acute surgical or traumatic injury to this area, is as follows: After the acute injury the initial effect is the immediate development of a polyuric, polydipsic syndrome indistinguishable from the full-blown disorder. Within hours to days this polyuric syndrome is replaced by a progressive reduction in urinary volume approaching the control level in both concentration and value, and the animal appears to be normal once again. During this *normal interphase,* however, the administration of an acute or sustained water load will not cause a normal water diuresis. The animal will continue to excrete little and inappropriately concentrated urine. If one persists in administering water, a state of profound hyposmolality and water intoxication will ensue. In

a matter of days the normal interphase will be replaced by a progressive increase in polyuria and polydipsia until a sustained state of DI is attained. The latter may be permanent or temporary, complete or partial. It is difficult to be certain about the exact cause of the first and second phases of this triphasic response. The initial, temporary DI-like state probably represents a physiologic lesion comparable to spinal shock; that is, as a consequence of the sudden injury to the axons or nerve cell bodies, all impulses responsible for discharge of the hormone from the neurohypophysis are eliminated and the hormone is not discharged into the circulation. On the basis of chemical analysis of the hypothalamus and neural lobe, it appears that during the normal interphase there is a slow "leak" of AVP from the injured axons and the neurohypophysis itself into the circulation as the neurohypophysis undergoes atrophy and its hormone content disappears.[189] Extensive lesions also produce a progressive disappearance of the hormone content of the hypothalamus itself.[189] If at the time of the initial experimental injury the stalk, posterior lobe and median eminence are removed, the normal interphase will not develop.[190] Finally, in the third phase the sustained state of DI is attained.

In those instances in which the lesion does not destroy or lead to the degeneration of the supraopticohypophyseal nuclei, the animal or patient may be left with the incomplete DI syndrome. This condition may manifest itself as a less severe polyuria (3,000 to 6,000 ml per day), with an impaired but not necessarily absent response to various osmotic and nonosmotic stimuli. At times this type of patient may fail to respond to hypertonic saline, but will develop a distinct antidiuresis after administration of acetylcholine or methacholine chloride (Mecholyl).[38,191,192] The triphasic response may be seen in many instances of pituitary stalk section, total hypophysectomy, cryohypophysectomy or even yttrium implantation. Figure 30 is a summary of metabolic changes in a patient who developed water intoxication and severe hyponatremia during the normal interphase of a mild DI which followed pituitary stalk section. This syndrome can be quickly differentiated from the impaired water excretion of acute glucocorticoid deficiency by giving the patient liberal amounts of cortisol or its equivalent. This therapy will immediately correct the water retention and hyponatremia if a glucocorticoid deficit exists. If it does not, the water retention of the

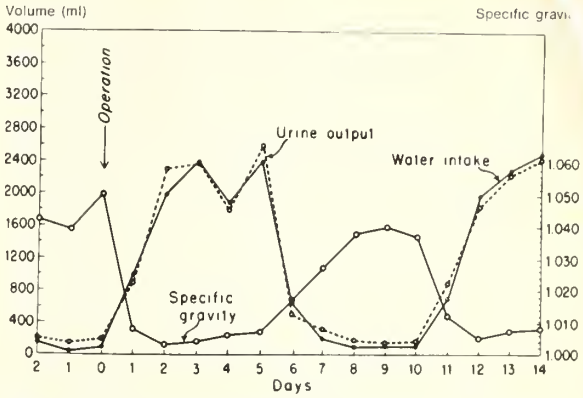

Figure 29.—Typical triphasic cycle produced by section of the hypophyseal stalk and damage to the median eminence. The interphase extends from day 6 to day 10 or 11. (Reproduced with permission from Hollinshead WH: Proc Mayo Clin 39:95, 1964.)

normal interphase will persist and only rigid water restriction will correct it.

Etiology

The following are the major causes of DI in their relative order of frequency: (1) idiopathic (approximately 50 percent), which may appear in a congenital and familial form; (2) posthypophysectomy (surgical, yttrium implants, cryohypophysectomy or stalk section); (3) basal skull fractures; (4) suprasellar and intrasellar tumors, either primary or metastatic, such as suprasellar cysts, craniopharyngioma, pinealoma, carcinoma of the breast and leukemia; (5) histiocytosis, such as eosinophilic granuloma and Schüller-Christian disease; (6) granulomatous disease, such as sarcoidosis and tuberculosis; (7) vascular lesions, such as aneurysms and atherosclerotic thrombosis; (8) encephalitis or meningitis, and (9) intraventricular hemorrhage.[193]

Idiopathic or primary DI may be a familial disease; the hereditary form has been described as autosomal dominant with incomplete female penetrance, or else an X-linked recessive. This form may appear at any time during the lifetime of a person. Although few postmortem investigations have been carried out, a recent study by Braverman and his associates has shown that this disorder was due to a substantial decrease in the number of nerve cells of the supraoptic and paraventricular nuclei with increased gliosis (Figure 31) and decreased size of the posterior pituitary.[194] The histologic changes observed in patients with idiopathic DI are in striking contrast to the intact and enlarged supraoptic nuclei with-

out gliosis seen in rats with hereditary congenital DI. In rats there is a defect in hormone synthesis and in humans, a degeneration of the hormone-producing cells. The cause of this degeneration and gliosis is completely unknown. These cases do not show any associated abnormality of anterior pituitary function.

The various types of therapeutic hypophysectomy are becoming an increasingly common iatrogenic cause of DI. Of the primary tumors, in the region of the neurohypophysis the adenomas of the anterior pituitary almost never cause DI. This is consistent with the experimental observation that removal of the posterior lobe per se does not result in DI. Those tumors that do create such a state must do so by involving the supraoptic and paraventricular nuclei or a major part of the neurohypophyseal stalk. The most classic examples of this are craniopharyngiomas and suprasellar cysts. On rare occasions, an acute DI state will develop as a result of metastases to the neurohypophyseal system. By far, the most common of these malignancies is carcinoma of the breast. Usually the DI develops late in the course of the disease and is almost always associated with other metastatic lesions. However, it may be the first subjective evidence of metastases. With this or

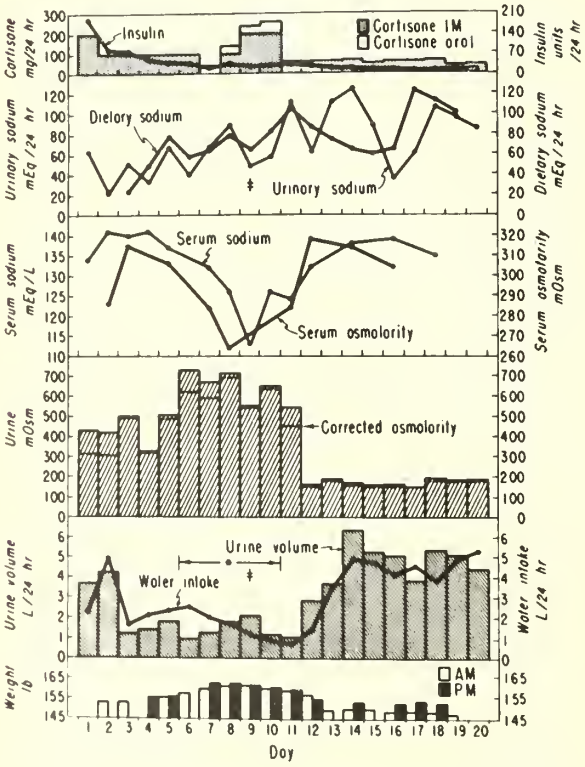

Figure 30.—Metabolic changes after pituitary stalk section in a 39-year-old woman. Asterisk shows period of confusion, headache and lethargy. Double dagger indicates intravenous administration of 385 mEq of sodium chloride as a 5 percent solution. (Reproduced with permission from Gastineau CF, et al: Proc Mayo Clin 42:406, 1967.)

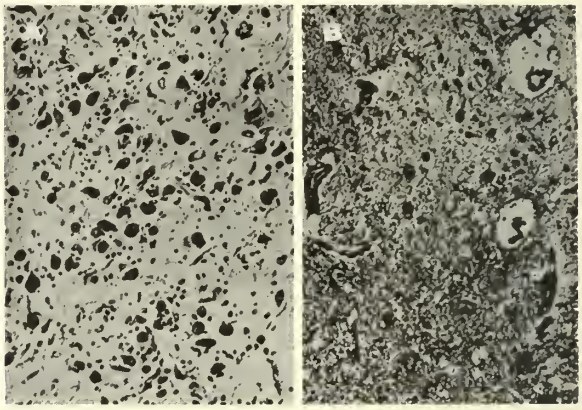

Figure 31.—Photomicrograph of supraoptic nucleus of a normal 52-year-old man **(A)** and of a patient with diabetes insipidus **(B)**. Note, in the normal subject, the large number of nerve cells with prominent peripheral distribution of Nissl substance. In the patient with diabetes insipidus there is a loss of nerve cells, a loss of Nissl substance and moderate gliosis (reduced from ×200). (Reproduced with permission from Braverman et al.[194])

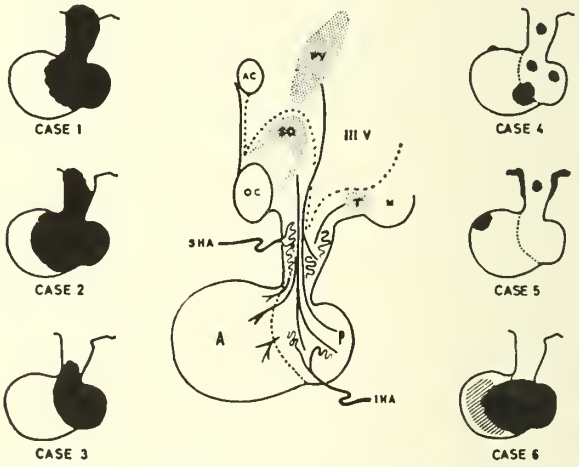

Figure 32.—Diagram of neural and vascular connections between hypothalamus and pituitary gland (center) and of the location of carcinomatous deposits (solid black) in six cases. The metastases are mainly in neural tissue at the sites of the primary capillary beds. In case 6, the stalk had been transected and the hatched area indicates the extent of infarction of the anterior lobe. A = anterior lobe; AC = anterior commissure; IHA = inferior hypophyseal artery; M = mammillary body; OC = optic chiasma; P = posterior lobe; PV = paraventricular nucleus; SHA = superior hypophyseal artery; SO = supraoptic nucleus; T = tubular nucleus; III V = third ventricle. (Reproduced with permission from Duchen.[192])

other malignant tumors metastasizing to the area, DI always precedes the development of anterior pituitary insufficiency, if the latter occurs. The tumor involves the anterior pituitary by contiguous spread from the neurohypophyseal system rather than by direct bloodstream metastasis to the adenohypophysis. As illustrated in Figure 32 (from the excellent study by Duchen[192]), the anterior lobe receives its blood supply through a portal circulation, whereas the neurohypophyseal system is supplied by the systemic circulation. Tumor cells would not readily gain entrance to this portal circulation. When DI develops in a given patient, every effort should be made to determine its cause, as it may be amenable to specific therapy. The DI may be accompanied by symptoms of the causative disorder, such as sarcoidosis, central nervous system tumor or xanthomatosis.

Clinical Features

Diabetes insipidus may occur at any age, and there is no sexual predilection. Because of the rare familial nature of the disorder, other family members should be evaluated if a patient develops the idiopathic type. Almost all cases of true DI are of abrupt onset. These patients often recall that the polyuria and thirst started suddenly and reached a peak in a day or two. The history of a gradually increasing urinary flow, over weeks to months, generally suggests some other polyuric disorder. Continuous thirst is, of course, a classic symptom of the disease—the patient showing a predilection for very cold or iced water. This desire for very cold water is not characteristic of other polyuric syndromes, including psychogenic polydipsia. The urinary volume may range between 3,000 and 15,000 ml per day, and a prominent nocturia is almost invariably present.

Patients with psychogenic polydipsia are rarely bothered with nocturnal polyuria. It must be remembered, however, that with DI of long duration the patients may develop an incredibly large caliceal, ureteral and bladder capacity with frank hydronephrosis and hydroureter. The muscular wall of the bladder becomes thinned and decreased in tone. These patients may void as much as 1,000 ml at a time, and the absence of nocturia, or the presence of only a mild nocturia, may be due to these alterations in the character and capacity of the urinary drainage system. On rare occasions, the hydronephrosis may lead to definite impairment of kidney function with elevated levels of blood urea nitrogen (BUN) and serum creatinine.[196] Diabetes insipidus may occasionally present in an atypical fashion. In one instance, the earliest symptom of DI in a young boy was the presence of severe night sweats. Nocturia did not occur because of dilatation of the urinary collecting system.[195]

Characteristically, the withdrawal of water from a patient with severe DI will lead to an extremely rapid weight loss, profound thirst and the rapid development of hypertonic dehydration. However, as long as the patient can satisfy this thirst, he or she will experience little but the inconvenience of the polyuria, and the state of hydration will remain close to normal.

Diagnosis

One must differentiate DI from all other important polyuric syndromes (Table 11). In DI, with the exception of mild plasma hyperosmolality (5 percent above normal), and unless pronounced dehydration is present, the blood and urinary chemistries are normal. This will not be the case in many of the syndromes listed in Table 11. A knowledge of the physiologic basis for polyuria is most helpful when one is confronted with this symptom.

True polyuria invariably means a decrease in the percentage of the filtered water that is absorbed by the renal tubules. This decrease may be secondary to an alteration in the tubular handling of water per se, to an impaired resorption of solutes with the development of an osmotic type of diuresis or, finally, as in most acquired renal diseases, to a combination of both of these functional abnormalities. The classification in Table 11 is relatively self-explanatory, and when physicians are confronted with a polyuric syndrome, they should consider most of the disorders listed. Polyuria may be the consequence of excessive water ingestion. Compulsive water drinking may be seen as a reflection of an underlying psychiatric disorder. Severe water intoxication to the point of death has been observed on occasion in severely disturbed or psychotic patients. The precise cause of this disturbance is not known. It is also possible that selective lesions in the hypothalamus can produce enhanced thirst such as those that occur after experimental stimulation of the hypothalamus in goats. Indeed, primary polydipsia has been reported in a patient with histiocytosis, which may reflect the influence of an organic lesion on water balance.[197] Alterna-

tively, endogenous dipsogens such as angiotensin II[198] or PGE may play a role in some of these patients. Thus, compulsive water drinking could have a psychologic, structural or neurochemical cause.

Nephrogenic diabetes insipidus (NDI) or vasopressin-resistant DI is a rare congenital and familial disorder in which, in the homozygous form, the renal tubules are totally refractory to the antidiuretic effect of vasopressin.[199-202] It is fascinating that although spontaneous mutation may rarely be the cause of this disorder,[200,201] all affected persons may have been of common genetic origin, descendants of an Ulster Scotsman.[202] In the heterozygous form or in the absence of complete penetrance, there may be varying degrees of responsiveness to AVP and, in turn, varying degrees of polyuria. When basal plasma AVP and osmolality are measured in these patients, they are usually found to be above normal,[94,203] suggesting a state of mild water depletion. The patient with NDI is clinically indistinguishable from one with DI until a complete, or almost complete, lack of response to Pitressin is observed. The exact cause of this defect in the nephron is unknown. Any step, from the initial binding of vasopressin to its receptor sites to the final metabolic event responsible for the maximum increase in the permeability of the distal nephron to water, could be defective. When the GFR and renal blood flow of patients with NDI are reduced to a degree comparable to that of patients with DI, the former are unable to produce a urine hypertonic to the plasma.[199] This suggests that in NDI the collecting duct is truly impermeable to water or that the renal medulla of these patients is either isotonic or even less hypertonic than the reduced medullary osmolality observed in the animal with DI.

The diagnosis of acquired nephrogenic diabetes insipidus should be restricted to patients with an acquired renal disorder whose polyuria is associated with a *persistently hypotonic* urine unresponsive to Pitressin or hydropenia. In general, the disorders (Table 12) do not attain the degree of polyuria observed in DI or NDI because, in most, the overall functioning renal mass is reduced by the basic disease process.

In DI a moderate concentration defect is usually present which can be corrected by the continuous administration of Pitressin. Valtin[72] found that the correction of the defect in congenital DI rats receiving Pitressin was associated with a return of the medulla to its maximally hyperosmolar state. The latter was due especially to a rise in urea concentration and, to some extent, NaCl. Invariably, in the DI patients or animals, urine volume will decrease substantially following a single injection of Pitressin, even though urinary osmolality, at first, may only slightly exceed isotonicity (that is, 450 mOsm per liter).

The diagnosis of DI is assured when it has been shown that one or more of the major stimuli to the release of AVP, such as carefully controlled water restriction, hypertonic saline infusions and

TABLE 11.—*Major Polyuric Syndromes Due to a Decrease in Tubular Reabsorption of Water and Solutes*

Water

Excessive water ingestion—minimal circulation of arginine vasopressin (AVP)
- Psychogenic polydipsia
- Polydipsia due to injury to hypothalamic thirst centers (rare)
- Potassium depletion and hypercalcemia
- Pronounced hyperreninemia (uncommon)

Inability to reabsorb adequate amounts of filtered water
- Inadequate circulation of AVP equals complete or partial AVP-responsive diabetes insipidus (DI)
- Renal tubular failure to respond normally to AVP
  - Nephrogenic DI (congenital and familial)
  - Nephrogenic DI (acquired)
    - Usual chronic renal diseases that do not primarily involve the glomerulus, such as chronic pyelonephritis, polycystic kidneys, analgesic nephropathy, gouty nephropathy, medullary cystic disease, all acute and chronic interstitial nephropathies
    - Obstructive uropathy
    - Multiple myeloma
    - Amyloid disease
    - The Sjögren syndrome
    - Potassium deficiency
    - Hyperaldosteronism or mineralocorticoid excess
    - Nephrocalcinosis or renal damage secondary to hypercalcemia
    - Unilateral renal artery occlusion (acute) with pronounced hyperreninemia
    - Diuretic phase of acute tubular necrosis (ATN) or nonoliguric ATN
    - Postrenal transplantation
    - Prostaglandin E excess acting on distal nephron may contribute to any of the above
    - Sickle-cell anemia
    - Ingestion of high doses of lithium
    - Methoxyflurane anesthesia
    - Dichlormethyltetracycline (Declomycin)

Solutes

Inability to reabsorb adequate quantities of filtered solutes (osmotic-type diuresis)
- Glucose—diabetes mellitus
- Salts—Primarily sodium chloride
- Urea—tissue catabolism or excess production of urea from hyperalimentation
  - Various types of chronic renal disease, particularly chronic pyelonephritis
  - After various diuretics, including mannitol

TABLE 12.—*Primary Water Depletion and Other Hyperosmolar States*

Hypernatremia and hyperosmolality with dehydration secondary to water loss in excess of sodium:

Polyuric states with failure of renal conservation of water in association with inadequate water intake

- Diabetes insipidus (DI), nephrogenic DI (congenital and acquired)
- Osmotic diuresis with unreplaced loss of hypotonic urine; pronounced glycosuria, mannitol diuresis (may be hyperosmolar and hyponatremic), high-protein gavage to comatose patients (urea diuresis), chronic renal failure

Primary water depletion in excess of sodium with normal renal-concentrating mechanisms; comatose or disoriented patients with inadequate water intake, primary disorders of thirst regulation, diabetic coma, excess sweating and diarrheal disorders in children, hypothalamic lesions causing adipsia or hypodipsia in which forced fluid administration corrected the hyperosmolar syndrome

Hypertonic peritoneal dialysis

Hypernatremia and hyperosmolality with possible normal hydration:

Reset of osmoregulatory center with or without hypodipsia (idiopathic, hydrocephalus, brain tumor, histiocytosis X, postconcussive hyperosmolality)

Hypernatremia and hyperosmolality with overhydration:

Primary aldosteronism, the Cushing syndrome, congestive heart failure with tracheostomy, pneumonia; hypertonic saline enemas to infants, hypertonic saline given orally to infants, iatrogenic hypertonic saline administration to patients with chronic renal failure, inadvertent dialysis with hypertonic sodium solution, hypertonic (glucose) peritoneal dialysis

nicotine administration (rapidly smoking three or four cigarettes), do not cause a pronounced antidiuresis or the production of hypertonic urine, and that the kidney is responsive to exogenous AVP or Pitressin. Probably the most important and reliable test to show endogenous secretion of AVP is simple water restriction. This will lead to mild or moderate dehydration, and if complete DI is present, a hypotonic urine (specific gravity below 1.005) or osmolality substantially below the simultaneously measured plasma osmolality will continue to be formed in spite of the dehydration. Restriction of water intake in a patient with probable DI should be done only with great care while the patient is observed closely. A patient with a severe case may lose as much as 0.5 kg of body water per hour, and the test should be stopped if the patient loses 3 percent of body weight. It must be remembered that if the dehydration causes a major drop in GFR and solute excretion, oliguria and a slightly hypertonic urine may be formed even in the absence of AVP secretion. If a sensitive bioassay or immunoassay for

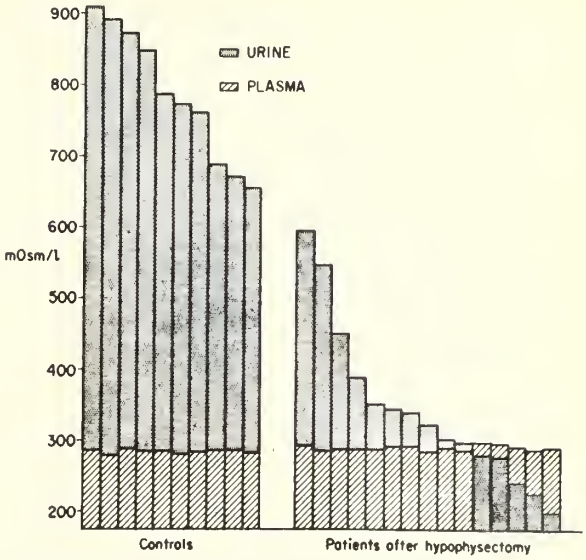

Figure 33.—Comparison of maximal urinary osmolality of normal controls with that of patients with varying degrees of diabetes insipidus following ten hours of water restriction. (Reproduced with permission from Lipsett & Pearson.[205])

AVP is available, it is possible to show that during water restriction the rise in plasma osmolality does not cause an appropriate rise in the level of AVP in the plasma[94,203,204] (see Figure 9 in Part I).

It has been generally thought that DI was an "all-or-nothing" disorder and that mild to moderate forms of DI did not exist. However, over 15 years ago Lipsett and Pearson[205] clearly illustrated that incomplete failure of production or release of AVP occurred clinically. Their patients developed DI after surgical procedures involving the region of the neurohypophyseal system; this form is most apt to be seen following such operations. Figure 33 shows maximal concentration of the urine compared with simultaneous plasma osmolality in subjects with varying degrees of posthypophysectomy DI following mild dehydration (ten hours of water restriction). It is apparent that a hypertonic urine can be formed by some of these patients, although they are not capable of producing a urine with an osmolality in the normal range for this test. The diagnosis of DI is obvious in those patients whose urine was distinctly hypotonic at the end of the water restriction, but the presence of a moderately hypertonic urine after this period of water restriction does not rule out the diagnosis of partial DI. These patients, therefore, had a quantitative decrease in the release or production of AVP.

Recently, Miller and associates[206] studied the

maximal concentrating capacity, during standardized conditions of dehydration, for normal volunteers, normal subjects admitted to hospital and a wide variety of patients with diabetes insipidus. They clearly confirmed the observations of Lipsett and Pearson[205] as well as showing that the patients with partial and complete DI, after attaining their maximal but subnormal urinary concentration, still responded with a further increase in urinary osmolality after an injection of AVP (Figure 34). The normal subjects and patients with psychogenic polydipsia did not show this response to exogenous AVP at the end of their dehydration. Thus, the production of a mildly to moderately hypertonic urine during water restriction, followed by a further significant increase in urinary osmolality (greater than 9 percent) with an injection of Pitressin, indicates the presence of incomplete DI. The response of patients with DI to the sulfonylurea chlorpropamide indicates that incomplete DI is far more common than ever suspected.

Rarely, a patient with a syndrome indistinguishable from DI may be unable to form a concentrated urine during simple dehydration or after the administration of hypertonic salt, but is able to produce a hypertonic urine after the administration of nicotine, a strong nonosmotic stimulus to the release of AVP. This would suggest that the subject is incapable of responding to an osmotic stimulus but may respond to a nonosmotic one. However, it should be stressed that nicotine frequently produces such reactions as nausea, vomiting and, at times, a substantial drop in blood pressure. Such an intense nonosmotic stimulus to the neurohypophyseal system would be quantitatively a far greater signal to its receptor and releasing function than the standard dehydration or hypertonic saline test. Therefore, we may not be dealing with a truly qualitative difference but, rather, with degrees of quantitative unresponsiveness. Furthermore, this pronounced reaction to nicotine may produce a considerable alteration in renal hemodynamics. If the patient does have such a subjective reaction in association with a definite antidiuretic response, a substantially concentrated urine (greater than 450 mOsm per liter) might also be formed even if the patient had not released AVP with this stimulus.

This type of patient will still be polyuric because the total secretion of AVP per day is less than that necessary to bring about normal homeostatic renal conservation of free water, and would be classified as incomplete DI with the ability to

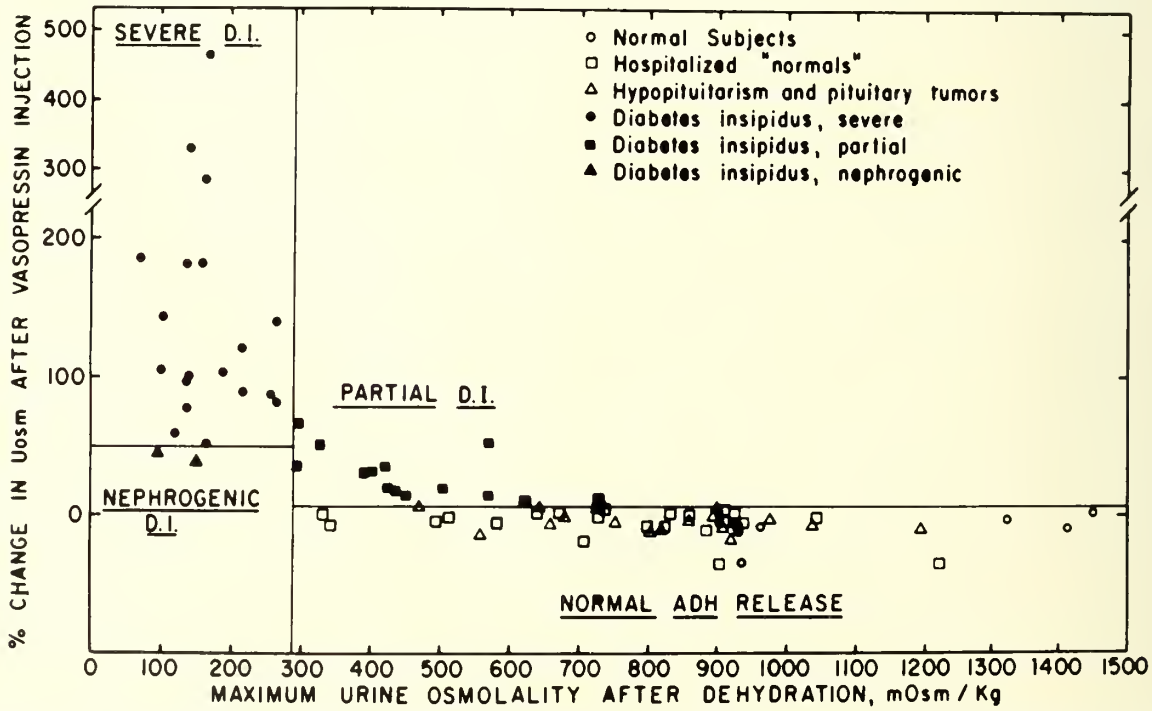

Figure 34.—The relationship between maximal urinary osmolality after dehydration in normal subjects as well as in patients with vasopressin-sensitive (pituitary) diabetes insipidus (DI) and with vasopressin-insensitive (nephrogenic) diabetes insipidus and the change in urinary osmolality after an injection of antidiuretic hormone. (From Miller et al.[206])

release AVP in response to a strong nonosmotic stimulus. It is possible that if every patient with DI were tested for his or her response to various *nonosmotic* (see Table 3 in Part I) as well as to the usual osmotic stimuli (dehydration and hypertonic saline), we would find many more patients with qualitative as well as quantitative defects in the ability to release AVP. De Rubertis and associates[38] described in remarkable detail another type of qualitative abnormality in AVP secretion in which a patient had little or no response to osmotic stimuli, but had an excellent response to various nonosmotic volume or baroreceptor stimuli. Enough AVP was secreted to prevent polyuria, but the patient had sustained hypernatremia and a deficit in thirst regulation.

In most patients with DI antidiuresis will not develop during or after the administration of hypertonic saline (5 grams per dl of NaCl) (Figure 35). For reasons cited earlier, subjects should not have too great a positive water load (that is, in excess of 500 ml) as they begin the test and probably should not receive more than 300 ml of 5 percent saline during the testing period. In normal subjects a distinct antidiuresis with hypertonic urine will develop within 30 to 60 minutes after starting the hypertonic saline infusion. Although the absence of an antidiuresis strongly suggests DI, it must be remembered that on rare occasions, in persons in whom a pronounced augmentation of salt excretion develops, the osmotic diuresis may be so great that there will be little or no drop in total urinary volume despite a distinct fall in free water clearance. The drop in free water clearance with the production of a hypertonic urine is a true measure of either a significant increase in permeability of the distal nephron or the presence of an effective amount of circulating AVP. The failure of a normal response to hypertonic saline, simple water withdrawal or nicotine (rapid smoking of three or four cigarettes) should be followed by the intravenous administration of Pitressin over two to three hours. If a hypertonic urine is formed, the diagnosis of DI is assured. A failure to produce a hypertonic urine after Pitressin administration does not absolutely rule out the diagnosis of DI, but suggests the possible presence of some functional or organic disorder of the renal tubules as the primary diagnosis.

The absence of significant polyuria does not necessarily rule out the diagnosis of DI. When GFR and solute excretion are substantially reduced (as in combined anterior and posterior pituitary insufficiency or severe water and salt depletion), and back diffusion of water occurs even in the absence of AVP, the urinary volume may be less than 3,000 ml per 24 hours, and urinary osmolality may approach or slightly exceed isotonicity.

In recent years several attempts to devise more simplified tests for the diagnosis of DI have appeared.[207] Basically, these have consisted of a standard period of rigid water restriction, varying

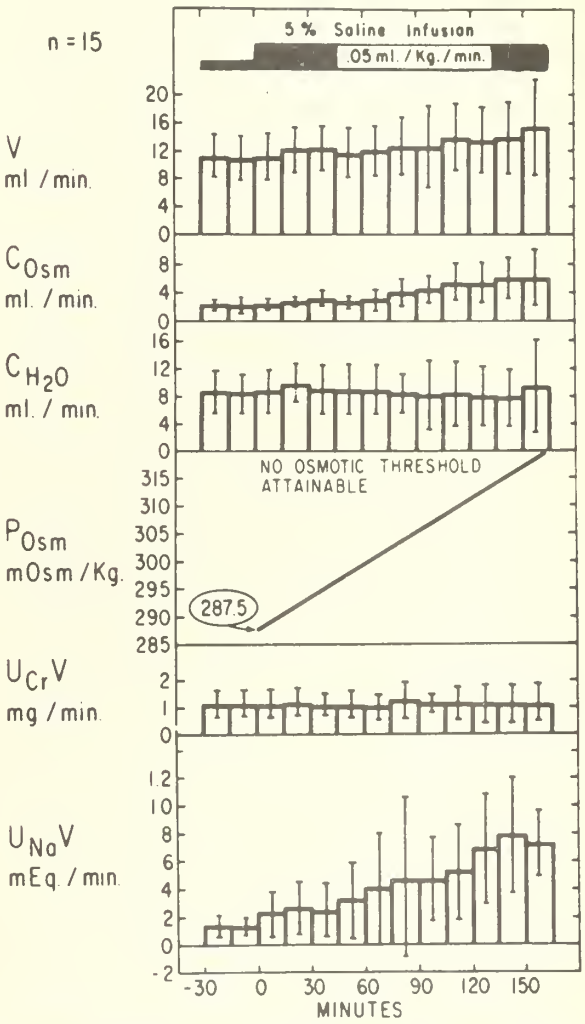

Figure 35.—Composite of 15 osmotic threshold studies in ten subjects with diabetes insipidus, of whom six had combined pituitary deficiency. No osmotic threshold was attainable even though the experiments were continued until the highest plasma osmolality in each instance ranged from 298 to 332 mOsm per kg. Time intervals are expressed in relation to the beginning of rapid saline infusion. V = volume; C_{Osm} = osmolar clearance; C_{H_2O} = free water clearance; P_{Osm} = plasma osmolality; $U_{Cr}V$ = creatinine excretion; $U_{Na}V$ = sodium excretion. (Reproduced with permission from Moses AM, et al: Am J Med 42:368-377, 1967.)

from six to eight hours, with a measure of plasma and urinary osmolality at the beginning and end of this period. Normal persons will have little or no change in their plasma osmolality; they will frequently begin with a moderately hypertonic urine which will become more concentrated by the end of the period of water restriction; that is, the U/P osmolality ratio will always significantly exceed 1 and, frequently, 2. A patient with complete DI will initiate the test with a plasma osmolality that on a random specimen *usually exceeds that of the normal subject;* the patient's initial urine osmolality will be less concentrated than plasma, and after six to eight hours of water restriction, the plasma osmolality may rise significantly with little or no change in urinary osmolality. Therefore, the U/P ratio does not go up and may actually fall. This test, if unequivocally positive, is strong presumptive evidence for the diagnosis of DI. However, the authors prefer in any given case to carry out the more extensive procedures described earlier. Too many patients have been misdiagnosed as having DI and have needlessly taken injections of Pitressin for months or sometimes years.

In patients with psychogenic polydipsia, as a consequence of the profound and sustained primary ingestion of water, *the random plasma osmolality is usually significantly below that of normal persons and certainly lower than that of patients with* DI. In patients with psychogenic polydipsia, in whom water is restricted under careful observation for 12 to 18 hours, urine volume will always be reduced to a low level (1 to 2 ml per minute) and urinary osmolality will increase at least to isotonicity. On occasion, however, a compulsive water drinker may be so overhydrated that it may require longer than 24 hours for the positive water load to be excreted and, therefore, a longer time for the urine volume to be reduced to a low level. This patient can usually be suspected because initial plasma osmolality and sodium concentration values will be considerably below normal. Patients with psychogenic polydipsia when given an infusion of hypertonic saline will respond like normal subjects with the single exception that maximal urinary osmolality will be less hypertonic. In the authors' experience, despite the concentrating defect resulting from months and years of excessive water ingestion, patients with psychogenic polydipsia can invariably concentrate at least to isotonicity. This response to dehydration and hypertonic saline administration readily differentiates these patients from those with complete DI. Incomplete DI may cause a problem in differential diagnosis, but the clinical picture, as described previously, the response to Pitressin after a period of dehydration,[201] and the progressive improvement in concentrating ability with modest water restriction in patients with psychogenic polydipsia will usually confirm the true diagnosis.

The authors have observed that patients with DI, under the influence of a maximal sustained water diuresis, do not generally produce a urine quite so dilute or so high in volume as normal subjects under similar circumstances, and random samples of their urine obtained when they are not receiving AVP are usually less dilute than during a sustained intravenously infused water load. This suggests that in patients with DI some new mechanism develops for either delivering a smaller volume of salt and water to the diluting segments of the nephron, or, less likely, for allowing a greater degree of back diffusion of water in these segments even in the absence of AVP.

Treatment

Once the diagnosis of DI has definitely been established, every effort should be made to find and treat the underlying causative disorder. Although newer modes of therapy are now available for treating DI some form of AVP administration frequently remains the mainstay of therapy; at present, the most common form is Pitressin Tannate in Oil (5 units per ml). There is a general tendency among physicians to use excessive doses of this drug. As little as 0.5 ml every two days, given as a deep intramuscular injection, is usually adequate for optimal control. Unfortunately, Pitressin Tannate is packed in 1-ml ampules, but the residual 0.5 ml may be covered with an alcohol sponge and adhesive and stored in the refrigerator for use later. If one looks carefully at an ampule of Pitressin Tannate, one can see a patch of dirty-brown material on the bottom of the ampule—this is the hormone. The ampule must be warmed in the hand and thoroughly shaken until this material is suspended in a slightly discolored emulsion. The importance of doing this cannot be emphasized too greatly. A small percentage of patients will have an occasional allergic or local reaction to this preparation. If this occurs, a period of desensitization may be instituted, beginning with a dosage of 0.01 ml per day or less, and gradually increasing it in step-

wise fashion. Antihistaminics may be administered simultaneously.

During the first days of treatment, and for emergency or acute use, aqueous Pitressin (20 units per ml) may be administered subcutaneously, particularly when DI complicates an acute disorder such as basal skull fracture or surgical (or nonsurgical) hypophysectomy. Use of Pitressin Tannate in Oil, with its effect taking place 24 to 48 hours after administration, makes it difficult to follow the unpredictable course of the DI complication. Also, water intoxication is more likely to develop in patients treated with the combination of the long-acting preparation and parenteral water administration. Recently, the authors observed a 30-year-old man who had been given Pitressin Tannate in Oil *(1 ml three times a day)* for acute DI associated with a basal skull fracture, a dosage which he then continued to take for two years. On his admission to hospital, laboratory studies gave the following values: serum sodium was 120 mEq per liter with a proportionate decrease in plasma osmolality and urine osmolality was 300 mOsm per liter. When administration of Pitressin Tannate was stopped, the patient had a profound diuresis of very hypotonic urine and lost 20 pounds in 24 hours. Values for serum sodium and osmolality tests returned to normal. He was shown on subsequent testing to have recovered completely from the DI, and the only abnormality was a functional concentrating defect resulting from the prolonged overhydration. This defect was corrected after four days of moderate water restriction (1,000 ml per day).

The usual dosage of aqueous Pitressin is 0.1 to 0.3 ml every four to six hours. One should be careful in administering these amounts to patients with known coronary artery disease because of the vasoconstrictive effect of this hormone.

Diapid, a nasal spray of synthetic lysine-8-vasopressin (50 units per ml, in isotonic saline) has been available for clinical use for almost a decade.[208] In contrast to arginine-8-vasopressin, lysine-8-vasopressin is remarkably stable; therefore, although not quite as potent as arginine-8-vasopressin, it lends itself admirably to use as a nasal spray. Studies indicate that this preparation is both stable and nontoxic, and when used approximately every four hours may cause a 50 percent to 75 percent reduction in urinary flow in the average case of DI. The nonirritating saline solution is sprayed deeply into the nasal passages from a plastic squeeze bottle, one to two sprays in each nostril. In the most severe cases of DI, it has been necessary to combine the nasal spray with the far less frequent use of Pitressin Tannate in Oil.

A newly developed synthetic analogue of vasopressin, dDAVP (1-desamino, 8-D-arginine vasopressin), in which the L-arginine in position 8 has been replaced by D-arginine, and the free amino group in position 1 has been removed. This remarkable analogue has greater antidiuretic degree and duration potency than the natural hormone or any other known analogue, whereas pressor activity in therapeutic doses has been reduced to very low values.[209-211] The reduced pressor activity of this compound permits administration of high doses via the nasal passages without the smooth muscle constricting effects of either AVP or LVP that often lead to abdominal cramps or hypertension. It appears to be six to ten times more potent than aqueous Pitressin, depending on the dose, is very stable and can be administered as nasal drops. A dose of 5 to 20 μg of dDAVP given as a nasal spray will result in 8 to 20 hours of antidiuresis in patients with central DI. The introduction of this highly potent, long-lasting AVP analogue dramatically changes the therapeutic options for patients with diabetes insipidus. It is certain that it will become the drug of choice for this disorder, and will thus eliminate the necessity for nonhormonal forms of therapy.

In recent years two nonhormonal forms of therapy have been developed for the treatment of DI: (1) various diuretics, primarily thiazides and (2) oral hypoglycemic agents such as chlorpropamide (Diabinese). The former has also made a major contribution to the treatment of NDI as no other successful treatment for this disorder had existed in the past. Crawford and Kennedy[212] first showed that chronic administration of thiazide diuretics to patients with NDI and DI could reduce urinary volume by approximately 50 percent in 24 hours and cause a comparable amelioration of thirst as well. The reduced urine volume, although less hypotonic, was never hypertonic. This suggested that the thiazides did not act by substantially increasing the permeability of the distal convoluted tubule or collecting duct. Recent studies have clearly shown, however, that other diuretics, as well as rigid sodium restriction, may cause a comparable degree of antidiuresis in these patients. Conversely, when a thiazide or other diuretic agent is administered with enough sodium chloride to prevent a negative salt balance

or a reduction in extracellular volume, the antidiuretic effect does not occur.[9,199] This implies that the mild negative salt balance and reduction of GFR, created by the diuretic, lead to enhanced reabsorption of isosmotic fluid in the proximal nephron. This, in turn, leads to a decrease in the amount of fluid delivered to the water-impermeable segments and, therefore, to a reduced urinary volume. Although diuretic therapy, particularly the use of thiazides, is now the specific form of therapy for NDI, it is at most an adjunct in the treatment of DI. The authors recommend this form of therapy in DI, either alone or in combination with the sulfonylureas, when a pronounced sensitivity to available vasopressins is present or if the polyuria is so severe that the AVP preparation must be administered too frequently to be practical as a form of therapy in itself. It is important to instruct the patient to restrict oral intake of sodium while on diuretics as the antidiuretic effectiveness of these agents is substantially reduced by ad libitum sodium.

While treating diabetes mellitus with the sulfonylurea chlorpropamide (Diabinese) in a patient with DI, Arduino and associates[213] noted that the nonglycosuric polyuria was considerably ameliorated. They clearly showed that this compound had an AVP-like effect and could be used successfully in the treatment of vasopressin-sensitive DI. It had no effect in nephrogenic DI. Since publication of these astute observations, numerous investigators have confirmed both the antidiuretic effect of chlorpropamide, which mimics small to moderate doses of AVP, and the therapeutic efficacy of chlorpropamide in many patients with DI.[214-221] Chlorpropamide acts through a mechanism(s) clearly different from that of the thiazides or other diuretics. The antidiuresis caused by the diuretics is secondary to their effect on sodium metabolism, and it is never accompanied by the production of a *hypertonic* urine. In contrast, when effective, a mild to moderate hypertonic urine is almost always produced by chlorpropamide and it has no known effects on sodium metabolism. It also does not alter the polyuria of nephrogenic DI, and the diuretics are as effective in NDI[213,214] as in DI. The use of another sulfonylurea hypoglycemic agent, tolbutamide, has, on rare occasions, also been associated with hyponatremia, but it is not as effective as chlorpropamide for the treatment of DI.[222]

An interesting clinical observation that may bear directly on the mechanism of the action of chlorpropamide is that some patients with DI do not respond to oral or parenteral administration of chlorpropamide. These patients appear to be those with the most severe or "complete" DI (patients who release no AVP from the neurohypophysis and, therefore, have none in the circulation). This suggests that the antidiuretic effect of these agents requires a minimal concentration of AVP in the circulation, a level which by itself has little, if any, antidiuretic action in the DI patient. In most clinical studies,[213-221] 50 percent to 80 percent of patients with DI respond in varying degrees to chlorpropamide therapy. Many of these patients, from the magnitude of their polyuria and failure to respond to antidiuretic stimuli, were considered to be patients with complete DI. Chlorpropamide responsiveness greatly broadens the spectrum and number of patients with incomplete DI. It further indicates that a maximal sustained water diuresis may be present in these patients and water-loaded, normal subjects,[221] despite the presence of minimal amounts of AVP in the circulation. These observations and the fact that chlorpropamide has no antidiuretic effect, but, rather, potentiates the action of nonantidiuretic doses of AVP in congenital DI rats,[223] indicate that chlorpropamide acts through a mechanism that augments or enhances the action of AVP on the distal nephron.

Ingelfinger and Hays[224] have carried out *in vitro* experiments on the toad bladder that also strongly suggest this conclusion. They found that chlorpropamide alone at concentrations as high as 3×10^2 mol had no effect on water movement across the toad bladder. This concentration is almost six times the mean blood level attained in patients on long-term therapy with 0.5 gram chlorpropamide. However, when vasopressin in a low concentration (6 mU per ml) was added to the bladders that had been incubated with the chlorpropamide, water movement was substantially greater than that of the paired controls receiving vasopressin alone. This enhancement was not seen when a high concentration of vasopressin (60 mU per ml) was used. Although chlorpropamide enhanced the action of vasopressin, it did not augment the effect of cAMP on water movement across the toad bladder. These observations led Ingelfinger and Hays to question whether the sulfonylureas exert a direct AVP-like effect on the kidney in DI, and to suggest that they acted by increasing the sensitivity of the distal tubule to trace amounts of vasopressin or vasopressin-like

peptides that persist in some patients with DI. They concluded from their observations that vasopressin and chlorpropamide share at least one site of action, and that this common site may precede cAMP within the receptor cell. This is supported by several *in vitro* studies in which chlorpropamide was shown to increase the activation of adenylate cyclase in the presence of submaximal concentrations of AVP.[225,226]

More recently, however, Brooker and Fichman[227] in an *in vitro* system found that sulfonylureas inhibit the cAMP phosphodiesterase, and thereby could increase the steady-state level of cAMP in tissues, depending on the tissue concentration achieved after oral or parenteral administration. As might have been anticipated from the present state of the art, Zusman and associates[183] most recently showed that chlorpropamide enhances the hydro-osmotic effect of AVP by inhibiting the AVP-stimulated tissue synthesis of PGE, a step proximal to and independent of the stimulation of the adenyl cyclase-cAMP system. As mentioned earlier, PGE appears to modulate the action of AVP on the nephron; for example, a rise in local PGE decreases the effectiveness of AVP while a fall increases the antidiuretic response to AVP. Conversely, AVP stimulates PGE synthesis from the kidneys of the rabbit, normal rat, the Brattleboro rat and in the toad urinary bladder[183] by increasing the rate of release of the PGE precursor arachidonic acid from intracellular storage pools.[183] That the chlorpropamide has no antidiuretic effect in patients with congenital nephrogenic DI,[213,214] is consistent with Ingelfinger and Hays' concept[224] that vasopressin and chlorpropamide share a common site of action. In NDI patients, this site in the tubular epithelium is nonresponsive to these agents.

Miller and Moses[221] found a significant correlation between the ability of the patients with DI to reduce free water clearance in response to water deprivation and the ability to reduce the free water clearance in response to subsequent chlorpropamide treatment. Both ethanol and water loading were able to overcome the chlorpropamide-induced antidiuresis. Water deprivation while the patients were receiving chlorpropamide resulted in a further increase in urine concentration. Their data lend further insight to the concept that for chlorpropamide to produce an antidiuresis, some low level of endogenous antidiuretic hormone must be present. The single best explanation for its action is that chlorpropamide is capable of augmenting the action of nonantidiuretic or low submaximal levels of endogenous or exogenous AVP. No evidence for direct AVP-like action of chlorpropamide has been found, because the ability to respond to the drug appears to depend on the presence of the residual AVP-releasing capacity of the neurohypophyseal system. Available data have not ruled out the additional possibility that chlorpropamide can enhance the release of AVP from a normal or an abnormal neurohypophyseal system. Such a central action is suggested by the effect of chlorpropamide in restoration of thirst in patients with adipsia.[228] Miller and Moses[221] concluded from their observations that the response to water deprivation in a patient with DI may serve as a useful test to predict which patients are most likely to be benefited by treatment with chlorpropamide.

In adults, the dosage should be 250 mg once or twice per day and in children, a half to a third of this dosage, depending on the child's age. The antidiuretic effect should begin within the first day after ingestion of the drug, reaching peak effectiveness within three to four days.[213-221] However, the authors have observed an occasional patient who requires as long as seven days to attain maximal antidiuretic benefit. Urine flow may fall to as little as a third of the predrug level with the production of a moderately (300 to 600 mOsm per liter) hypertonic urine. When the response is optimal, chlorpropamide can be used as the sole form of therapy. In other patients it may be an important adjunct to the various forms of vasopressin. Because its mechanism of action differs from the thiazides, the two drugs will have additive effects and thereby complement each other therapeutically. An occasional patient, primarily one who appears to have complete DI, will not respond to maximal doses (500 to 750 mg per day) of chlorpropamide, and the drug should not be continued in such a patient. It is extremely important to remember that hypoglycemia may accompany the antidiuretic dose, especially during periods of fasting. The patient must be made aware of the hypoglycemic symptoms, and it is recommended that small between meal and bedtime feedings be taken. Excess water ingestion in patients with DI and even in non-DI patients with diabetes mellitus, ingesting sulfonylureas may cause hyponatremia and water intoxication;[68,219,229] this is because of the sustained effect of those agents on the distal nephron.

Clofibrate (Atromid) has also been shown to

exert an antidiuretic action in patients with DI who have some residual neurohypophyseal function.[230] This action appears to be mediated by enhanced secretion of endogenous AVP.[231] Clofibrate has the advantage of having considerably fewer side effects than chlorpropamide. Carbamazepine (Tegretol), a potent anticonvulsant also used for the treatment of tic douloureux, has been shown to be very effective in the oral therapy of DI.[232] Rado[233] has shown that this agent has a synergistic action when used along with chlorpropamide in patients who show an inadequate response to chlorpropamide alone.[231] Combined use of both agents permits lower doses of each agent to be used with less likelihood of dose-related toxicity. Kimura and co-workers have shown significant increases in bioassayable plasma AVP that were not fully suppressed by oral water loading after treatment with carbamazepine.[234] This suggested that the drug acted centrally to release AVP independently of osmotic stimulation. In contrast, Meinders and co-workers were unable to detect plasma AVP by immunoassay during the period of maximal antidiuresis after carbamazepine therapy in both patients with DI and in control subjects.[235] The explanation for this discrepancy is unclear. Carbamazepine does not appear to have any intrinsic antidiuretic activity nor does it augment submaximal doses of AVP.[236]

Needless to say, the well-treated patient with DI may lead a normal life in every respect. Untreated patients, as long as water is available and can be taken ad libitum, despite the inconvenience of the frequent day and night voidings, will suffer no basic ill effects and do remarkably well. However, if for any reason they are unable to ingest water or have it readily available, profound dehydration, water depletion and hyperosmolar syndrome may develop in a very short period of time.

A patient with DI who is receiving adequate amounts of vasopressin, other forms of therapy, or both, need not alter his or her diet in any manner. During the first few days or weeks of treatment the patient should be warned against continued excessive water ingestion because of the danger of water intoxication. In those cases in which the DI is frequently of a temporary nature, the therapy should be discontinued at intervals to note the patient's water turnover and possible recovery.

REFERENCES

1-142, see Part 1, Nov 1979 issue.

143. Kleeman CR, Vorherr H: Water metabolism and the neurohypophyseal hormones, *In*, Bondy PK, Rosenberg L (Eds): Duncan's Diseases of Metabolism. Philadelphia, WB Saunders Co, 1974

144. Rector FC Jr: Renal concentrating mechanisms, *In* Andreoli TE, Grantham JJ, Rector FC Jr, (Eds): Disturbances in Body Fluid Osmolality. Bethesda MD, American Physiology Society, 1977, chap 8, p 179

145. Schafer JA, Andreoli TE: Action of antidiuretic hormone on water and nonelectrolyte transport processes in mammalian collecting tubules, *In* Andreoli TE, Grantham JJ, Rector FC Jr (Eds): Disturbances in Body Fluid Osmolality. Bethesda MD, American Physiology Society, 1977, chap 3, p 57

146. Jamison RL, Maffly RH: The urinary concentrating mechanism. N Engl J Med 295:1059-1067, 1976

147. Hays RM, Levine SD: Pathophysiology of water metabolism, chap 1, *In* Brenner BM, Rector FC Jr (Eds): The Kidney. Philadelphia, WB Saunders Co, 1976, p 553

148. Tisher CC: Anatomy of the kidney, *In* Brenner BM, Rector FC Jr (Eds): The Kidney. Philadelphia, WB Saunders Co, 1976

149. Kriz W, Lever AF: Renal countercurrent mechanisms: Structure and function. Am Heart J 78:101-118, 1969

150. Kokko JP: Membrane characteristics governing salt and water transport in the loop of Henle. Fed Proc 33:24-30, 1974

151. Stephenson JL: Concentration of urine in a central core model of the renal counterflow system. Kidney Int 2:85-94, 1972

152. Stephenson JL: Concentrating engines and the kidney: I and II. Biophys J 13:512-546, 1973

153. Kokko JP, Rector FC Jr: Countercurrent multiplication system without active transport in inner medulla. Kidney Int 2: 214-223, 1972

154. Rocha AS, Koddo JP: Sodium chloride and water transport in the medullary thick ascending limb of Henle. J Clin Invest 52:612, 1973

155. Grantham JJ, Burg MB: Effect of vasopressin and cyclic AMP on permeability of isolated collecting tubules. Am J Physiol 211:255, 1966

156. Britton KE, Carson ER, Cage PE: A "bootstrap" model of the renal medulla. Postgrad Med J 52:279-284, 1976

157. Ullrich KJ, Jarausch KH: Untersuchungen zum Problem der Harn Konzentrierung und Verdünnung. Pflügers Arch Gesamte Physiol 262:537, 1956

158. Burg MB: Tubular chloride transport and the mode of action of some diuretics. Kidney Int 9:189-197, 1976

159. Pennell JP, Sanjana V, Frey NR: The effect of urea infusion on the urinary concentrating mechanism in protein depleted rats. J Clin Invest 55:399-409, 1975

160. Johnston PA, Battilana CA, Lacy FB, et al: Evidence for a concentration gradient favoring outward movement of sodium from the thin loop of Henle. J Clin Invest 59:234-240, 1977

161. Gertz KH, Schmidt-Nielsen B, Pagel D: Exchange of water, urea and salt between mammalian renal papilla and the surrounding urine (abstract). Fed Proc 25:327, 1966

162. Schütz W, Schnermann JP: Pelvic urine composition as a determinant of inner medullary solute concentration and urine osmolality. Pflügers Arch 334:154, 1972

163. Berliner RW, Bennett CM: Concentration of urine in the mammalian kidneys. Am J Med 42:777-789, 1967

164. Andreoli TE, Schafer JA: Mass transport across cell membranes: The effects of antidiuretic hormone on water and solute flows in epithelia, *In* Knobil E, Sonnenschein RR, Edelman IS (Eds): Annual Review of Physiology, Vol 38. Palo Alto CA, Annual Reviews, Inc, 1977, p 451

165. Hays RM: Antidiuretic hormone. N Engl J Med 292:659, 1976

166. Walter R, Clark WS, Mehta PK, et al: Conformational considerations of vasopressin as a guide to development of biological probes and therapeutic agents, *In* Andreoli TE, Grantham JJ, Rector FC Jr (Eds): Disturbances in Body Fluid Osmolality. Bethesda MD, American Physiology Society, 1977, chap 1, p 1

167. Handler JH, Orloff J: The mechanism of action of antidiuretic hormone, *In* Orloff J, Berliner RW (Eds): Handbook of Physiology, Sect. 8, Renal Physiology. Baltimore, Waverly Press, Inc, 1973, p 791

168. Dousa TP, Valtin H: Cellular actions of vasopressin in the mammalian kidney. Kidney Int 10:55-72, 1976

169. Kuo JF, Greengard P: Cyclic nucleotide dependent protein kinases—IV. Widespread occurrence of adenosine 3'5' monophosphate dependent protein kinase in various tissues and phyla of the animal kingdom. Proc Natl Acad Sci USA 64:1349-1355, 1969

170. Taylor A: Role of microtubules and microfilaments in the action of vasopressin, *In* Andreoli TE, Grantham JJ, Rector FC Jr (Eds): Disturbances in Body Fluid Osmolality. Bethesda MD, American Physiology Society, 1977, chap 5, p 97

171. Dousa TP, Barnes LD: Effects of colchicine and vinblastine on the cellular action of vasopressin in mammalian kidney—A possible role of microtubules. J Clin Invest 54:252-262, 1974

172. Kachadorian WA, Wade JB, Di Scala VA: Vasopressin induced structural change in toad bladder luminal membrane. Science 190:67-69, 1975

173. Kachadorian WA, Wade JB, Viterwyk CC, et al: Membrane structural and functional responses to vasopressin in toad bladder. J Membr Biol 30:381-401, 1977

174. Koefoed-Johnsen V, Ussing HH: The contributions of diffusion and flow to the passage of H_2O through living membranes. Acta Scand Physiol 28:60, 1953

175. Valtin H: Genetic models for hypothalamic and nephrogenic diabetes insipidus, *In* Andreoli TE, Grantham JJ, Rector FC Jr (Eds): Disturbances in Body Fluid Osmolality. Bethesda MD, The American Physiological Society, 1977, pp 197-216

176. Miller M, Moses AM: Radioimmunoassay of urine antidiuretic hormone with application to study of the Brattleboro rat. Endocrinology 88:1389-1396, 1971

177. Eknoyan G, Suki WN, Rector FC Jr, et al: Functional characteristics of the diluting segment of the dog nephron and the effect of extracellular volume expansion on its reabsorption capacity. J Clin Invest 46:1178, 1967

178. Jamison RL, Buerkert J, Lacy F: A micropuncture study of collecting tubule function in rats with hereditary diabetes insipidus. J Clin Invest 50:2444, 1971

179. Epstein FH, Kleeman CR, Hendriks A: The influence of bodily hydration on the renal concentrating process. J Clin Invest 36:629, 1957

180. Miller L, Fisch L, Kleeman CR: Relative potency of arginine-8-vasopressin and lysine vasopressin in humans. J Lab Clin Med 69:270-291, 1967

181. Kleeman CR, Levi J, Bettor O: Kidney and adrenocortical hormones. Nephron 15:261-278, 1975

182. Zusman RM, Keiser HR, Handler JS: Adrenal steroids enhance vasopressin stimulated water flow in the toad bladder by inhibiting prostaglandin E biosynthesis. Proc Am Soc Neph Mtg, Washington, DC, 1977, p 127A

183. Zusman RM, Keiser HR, Handler JS: A hypothesis for the molecular mechanism of action of chlorpropamide in the treatment of diabetes mellitus and diabetes insipidus. Fed Proc 36:2728-2729, 1977

184. Anderson RJ, Berl T, McDonald KM, et al: Evidence for an in vivo antagonism between vasopressin and prostaglandin in the mammalian kidney. J Clin Invest 56:420-426, 1975

185. Berl T, Raz A, Wald H, et al: Prostaglandin synthesis inhibition and the action of vasopressin: Studies in man and rat. Am J Physiol 232:F529-537, 1977

186. Galvez OG, Roberts BW, Bay WH, et al: Studies of the mechanism of polyuria with hypokalemia. Proc 9th Ann Mtg Am Soc Neph 1976, p 97

187. Goldberg M: The renal physiology of diuretics, *In* Orloff J, Berliner RW (Eds): Handbook of Physiology. Washington DC, American Physiology Society, 1973, pp 1003-1031

188. Kleeman CR, Cutler R: The neurohypophysis. Ann Rev Physiol 25:385-432, 1963

189. Laszlo FA, de Wied D: Antidiuretic hormone content of the hypothalamo-neurohypophyseal system and urinary excretion of antidiuretic hormone in rats during the development of diabetes insipidus after lesions in the pituitary stalk. J Endocrinol 36:125-137, 1966

190. Kovacs K, Laszlo FA, David MA: The antidiuretic phase of water metabolism in rats after lesions of the pituitary stalk—II. The role of the antidiuretic hormone. J Endocrinol 25:397-401, 1962

191. Vejjajiva A, Sitprija V, Shuangshoti S: Chronic sustained hypernatremia and hypovolemia in hypothalamic tumor—A physiologic study. Neurology 19:161-166, 1969

192. Duchen GW: Metastatic carcinoma in the pituitary gland and hypothalamus. J Pathol Bacteriol 91:347-355, 1966

193. Adams JM, Kenny JD, Rudolph AJ: Central diabetes insipidus following intraventricular hemorrhage. J Pediatr 88:292-294, 1976

194. Braverman LE, Mancini JP, McGoldrick DPM: Hereditary idiopathic diabetes insipidus—A case report with autopsy findings. Ann Intern Med 63:504-508, 1965

195. Raff SB, Greenberg H: Night sweats—A dominant symptom in diabetes insipidus. JAMA 234:1252-1253, 1975

196. Friedland GW, Axman MM, Russi MF, et al: Renal back pressure atrophy with compromised renal function due to diabetes insipidus—Case report. Radiology 98:359-360, 1971

197. Helbeck H, Krivit W, Nesbit ME: Patterns of antidiuretic function in diabetes insipidus caused by histiocytosis X. J Lab Clin Med 78:194-202, 1971

198. Rogers PW, Kurtzman NA: Renal failure—Uncontrollable thirst and hyperreninemia. JAMA 225:1236-1238, 1973

199. Cutler R, Kleeman CR, Maxwell MH, et al: Physiologic studies in nephrogenic diabetes insipidus. J Clin Endocrinol 22: 827-838, 1962

200. Feigin RD, Rimoin DL, Kaufman RL: Nephrogenic diabetes insipidus in a Negro kindred. Am J Dis Child 120:64-68, 1970

201. Kaplan SA, Yuceoglu AM, Strauss J: Vasopressin-resistant diabetes insipidus. Am J Dis Child 97:308-313, 1959

202. Bode HH, Crawford JD: Nephrogenic diabetes insipidus in North America: The Hopewell hypothesis. N Engl J Med 280: 750-754, 1969

203. Robertson GL: Immunoassay of plasma vasopressin in man. Proc Natl Acad Sci 66:1298-1305, 1970

204. Beardwell CG: Radioimmunoassay of arginine vasopressin in human plasma. J Clin Endocrinol Metab 33:254-260, 1971

205. Lipsett MB, Pearson OH: Further studies of diabetes insipidus following hypophysectomy in man. J Lab Clin Med 49:190-199, 1957

206. Miller M, Dalakos T, Moses AM, et al: Recognition of partial defects in antidiuretic hormone secretion. Ann Intern Med 73:721-729, 1970

207. Dashe AM, Cramm RE, Crist CA, et al: A water deprivation test for differential diagnosis of polyuria. JAMA 185:699-703, 1963

208. Dashe AM, Kleeman CR, Czaczkes JW, et al: Synthetic vasopressin nasal spray in the treatment of diabetes insipidus. JAMA 190:1069-1071, 1964

209. Vavra G, Machova A, Holecek V: Effect of synthetic analogue of vasopressin in animals and in patients with diabetes insipidus. Lancet 1:948-952, 1968

210. Robinson AG: DDAVP in the treatment of diabetes insipidus. N Engl J Med 294:507-511, 1976

211. Lee WP, Lippe BM, La Franchi SH, et al: Vasopressin analog DDAVP in the treatment of diabetes insipidus. Am J Dis Child 130:166-169, 1976

212. Crawford JD, Kennedy G: Chlorothiazide in diabetes insipidus. Nature 183:891-892, 1959

213. Arduino F, Ferraz FPJ, Rodrigues J: Antidiuretic action of chlorpropamide in idiopathic diabetes insipidus. J Clin Endocrinol Metab 26:1325-1328, 1966

214. Reforzo-Membrines J, Moledo LI, Lanaro AE, et al: Antidiuretic effect of 1-propyl-3-p-chlorobenzene-sulfonylurea (chlorpropamide). J Clin Endocrinol Metab 28:332-336, 1968

215. Kunstadter RH, Cabana EC, Oh W: Treatment of vasopressin-sensitive diabetes insipidus with chlorpropamide. Am J Dis Child 117:436-441, 1969

216. Zgliozynski S: Antidiuretic effect of sulfonylureas in idiopathic diabetes insipidus. Helvet Med Acta 34:478-485, 1969

217. Vallet HL, Prasad M, Goldbloom RB: Chlorpropamide treatment of diabetes insipidus in children. Pediatrics 45:246-253, 1970

218. Meinders AE, Touber JL, de Vries LA: Chlorpropamide treatment in diabetes insipidus. Lancet 2:544-546, 1967

219. Webster B, Bain J: Antidiuretic effect and complications of chlorpropamide therapy in diabetes insipidus. J Clin Endocrinol Metab 30:215-227, 1970

220. Berndt WO, Miller M, Kettyle WM, et al: Potentiation of the antidiuretic effect of vasopressin by chlorpropamide. Endocrinology 86:1028-1032, 1970

221. Miller M, Moses AM: Mechanism of chlorpropamide action in diabetes insipidus. J Clin Endocrinol Metab 30:488-496, 1970

222. Hagen GA, Frawley TF: Hyponatremia due to sulfonylurea compounds. J Clin Endocrinol Metab 31:570, 1970

223. Mahoney JH, Goodman DA: Hypernatremia due to hypodipsia and elevated threshold for vasopressin release—Effects of treatment with hydrochlorothiazide, chlorpropamide and tolbutamide. N Engl J Med 279:1191-1196, 1968

224. Ingelfinger JR, Hays RA: Evidence that chlorpropamide and vasopressin share a common site of action. J Clin Endocrinol Metab 29:738-740, 1969

225. Lozada ES, Gouaux J, Franki N, et al: Studies of the mode of action of the sulfonylureas and phenylacetamides in enhancing the action of vasopressin. J Clin Endocrinol Metab 34: 704-712, 1972

226. Beck N, Kim KS, Davis BB: Effect of chlorpropamide on cyclic AMP in rat renal medulla. Endocrinology 95:771-774, 1974

227. Brooker G, Fichman M: Chlorpropamide and tolbutamide inhibition of adenosine 3'5' cyclic monophosphate phosphodiesterase. Biochem Biophys Res Commun 42:824-828, 1971

228. Bode HH, Harley BM, Crawford JD: Restorational normal drinking behavior by chlorpropamide in patients with hypodipsia and diabetes insipidus. Am J Med 51:304-313, 1971

229. Weissman PN, Shenkman L, Gregerman RI: Chlorpropamide hyponatremia—Drug-induced inappropriate antidiuretic-hormone activity. N Engl J Med 284:65-71, 1971

230. de Gennes JL, Bertrand C, Bigorie B, et al: Etudes preliminaires de l'action antidiuretique du clofibrate (ou Atromid S) dans le diabete insipide pitressosensible. Ann Endocrinol 31:300-308, 1970

231. Moses AM, Howanitz J, Van Gemert M, et al: Clofibrate induced antidiuresis. J Clin Invest 52:535-542, 1973

232. Braunhofer J, Zicha L: Eröffnet Tegretal neue Therapiemöglichkeiten bei bestimmten neurologischen und endokrinen Krankheitsbildern? Med Welt 17:1875-1880, 1966

233. Rado JP: Combination of carbamazepine and chlorpropamide in the treatment of "hyporesponder" pituitary diabetes insipidus. J Clin Endocrinol Metab 38:1-7, 1974

234. Kimura T, Matsui K, Sato T, et al: Mechanism of carbamazepine (Tegretol) induced antidiuresis: Evidence for release of antidiuretic hormone and impaired excretion of a water load. J Clin Endocrinol Metab 38:356-362, 1974

235. Meinders AE, Cejka V, Robertson GL: The antidiuretic action of carbamazepine in man. Clin Sci Molec Med 47:289-299, 1974

236. Moses AM, Miller M: Drug-induced dilutional hyponatremia. N Engl J Med 291:1234-1239, 1974

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Symposium on Adolescent Gynecology and Endocrinology

Part II: Secondary Amenorrhea, Hirsutism in Adolescents and the Clinical Consequences of Stilbestrol Exposure *In Utero*

Secondary Amenorrhea

VAL DAVAJAN, MD*
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SECONDARY AMENORRHEA is commonly defined as the absence of menses for six months in a patient who has previously had regular menses, or the absence for 12 months in a patient with previous irregular menses. Before the differential diagnosis in these patients is considered, thyroid disease, diabetes mellitus, and normal or abnormal pregnancies should be ruled out with determinations of thyroid-stimulating hormone (TSH), triiodothyronine (T_3) and thyroxine (T_4); some assessment of thyroxin-binding globulin (by a T_3 resin uptake or immunoassay of the globulin); a fasting blood glucose determination, and a pregnancy test, preferably by the beta human chorionic gonadotropin radioimmunoassay method. If these tests give normal findings the patients may be divided into the following three categories: (1) patients with no evidence of galactorrhea, cortisol or androgen excess, (2) patients with galactorrhea or (3) those with possible cortisol excess (Cushing syndrome) or androgen excess (or both). Patients with androgen excess will be discussed in a separate section of this symposium. Only patients with amenorrhea with or without galactorrhea are discussed in this section.

Amenorrheic Patients Without Galactorrhea

Patients with amenorrhea and no clinical evidence of excess cortisol (Cushing syndrome) or androgen production or galactorrhea can first be divided into two groups based upon whether or not they have uterine bleeding following the intramuscular injection of 100 or 200 mg of progesterone-in-oil. The positive or negative response of the endometrium to progesterone has been shown to correlate with levels of serum estradiol.[37] For the test results to be considered positive, the amount of uterine bleeding can be minimal dark

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ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
DES = diethylstilbestrol
DHEA = dehydroepiandrosterone
FSH = follicle-stimulating hormone
GnRH = gonadotropin-releasing hormone
HMG = human menopausal gonadotropin
LH = luteinizing hormone
PCO = polycystic ovarian (disease)
PRL = prolactin
T_3 = triiodothyronine
T_4 = thyroxine
TeBG = testosterone-estradiol-binding globulin (sex steriod binding globulin)
TSH = thyroid-stimulating hormone

brown staining or a normal menstrual flow. When uterine bleeding takes place, it usually occurs between 3 and 14 days after the intramuscular injection. Amenorrhea in patients with normal breast development and an intact uterus may be due to hypothalamic-pituitary-ovarian dysfunction or uterine disease.

Hypothalamic Causes

- *Hypothalamic dysfunction*

One of the most common causes of amenorrhea is anovulation secondary to hypothalamic dysfunction without any history of stress or drug intake. The dysfunction may be due to failure of estradiol to rise sufficiently enough to trigger the luteinizing hormone (LH) surge. The primary defect may be a neurotransmitter derangement. In patients with this disorder levels of estradiol are at least 40 pg per ml and, therefore, uterine bleeding occurs following progesterone administration.[37] The serum follicle-stimulating hormone (FSH) and LH levels are in the normal range in these patients.

- *Hypothalamic dysfunction secondary to medications*

The drugs most commonly associated with amenorrhea are the phenothiazine derivatives and the contraceptive steroids. The action of the tranquilizers appears to be due to catecholamine depletion. Recent data have shown that contraceptive steroids have a suppressive effect on the pituitary in addition to their inhibitory effect on the hypothalamus.[38] In most of the patients with amenorrhea due to drugs there are normal serum FSH, LH and estradiol levels and, therefore, there will be uterine bleeding following progesterone administration.

- *Hypothalamic dysfunction secondary to stress*

In some patients amenorrhea will develop when a stress situation is encountered (for example, going away to school or divorce in the family). In these patients there most often are normal levels of FSH, LH and estradiol, and, therefore, uterine bleeding occurs following progesterone administration.

- *Hypothalamic failure secondary to either lesions of the hypothalamus or lack of GnRH synthesis*

These disorders are rare and may present as either primary or secondary amenorrhea. Lesions of the hypothalamus which have been associated with amenorrhea include craniopharyngioma, tuberculous granuloma and the sequelae of meningoencephalitis. In most patients with such disorders no demonstrable lesion can be found. The amenorrhea is most likely due to the lack of gonadotropin-releasing hormone (GnRH).[39] In these patients estradiol levels are low and uterine bleeding will not occur after progesterone administration. Randomly determined serum FSH and LH levels are either very low or in the low normal range, and are insufficient to stimulate the ovarian follicles to synthesize estradiol.

- *Hypothalamic amenorrhea secondary to weight loss*

This group includes patients with simple weight loss and anorexia nervosa.[40] Patients with simple weight loss are those who become amenorrheic after losing 15 percent to 20 percent of ideal body weight (usually referred to as being underweight) or those with greater than 25 percent weight loss who are considered to be severely underweight. In these persons there may be normal or low gonadotropin and estrogen levels depending on the degree of weight loss. Patients with anorexia nervosa in addition to having severe weight loss (greater than 25 percent of ideal body weight) have the added complaints of constipation, hypotension, bradycardia and hypothermia. These persons invariably have an abnormal ideation concerning their body image and have an aversion to food intake. They have low serum gonadotropin and estrogen levels. In addition, almost every patient with anorexia nervosa, in contrast to those with simple weight loss, has low serum T_3 and normal serum T_4 levels.

Treatment in these two groups of patients ap-

pears to be primarily related to regaining body weight. Patients with anorexia nervosa need psychiatric therapy.

Pituitary Causes of Amenorrhea

Patients with amenorrhea due to a pituitary abnormality may have nonneoplastic lesions or tumors.[37]

- *Nonneoplastic lesions of the pituitary*

This group includes patients with a destructive process of the pituitary such as that seen in the Sheehan syndrome due to postpartum hemorrhage. The pituitary cells are damaged either by anoxia, thrombosis or hemorrhage. These patients have low serum levels of LH, FSH and estradiol and, therefore, will not bleed following intramuscular injection of progesterone. Depending on the extent of the pituitary destruction, many of these patients also have hypothyroidism and adrenal insufficiency. These patients must have a total pituitary evaluation using insulin-induced hypoglycemia to evaluate their growth hormone, prolactin and adrenocorticotropic hormone (ACTH), which is measured indirectly by serum cortisol response. These patients may need thyroxin and glucocortocoid replacement therapy.

- *Pituitary tumors*

Amenorrhea may be the first sign of a pituitary tumor. Chromophobe adenomas are the most common pituitary tumor reported in association with amenorrhea. These tumors do not secrete hormones and should be considered as different tumors than prolactin-secreting adenomas which are associated with galactorrhea. Galactorrheic patients presenting with or without menstrual disorders are considered below.

Patients with amenorrhea secondary to pituitary tumors usually have low serum estrogen levels and, therefore, do not have uterine bleeding following intramuscular administration of progesterone. A random determination of serum levels of FSH and LH may give findings either low or normal. Therefore, polytomographic studies of the sella turcica must be obtained in all amenorrheic patients who do not have withdrawal bleeding and have either low or normal levels of serum FSH. If the patient is found to have a tumor, surgical operation or radiation (or both) is usually indicated. Use of replacement hormone therapy will be dependent on the functional status of the pituitary following therapy.

Ovarian Causes of Amenorrhea

There are four ovarian causes of amenorrhea listed in this section. Three of these disorders result in ovarian failure and include premature ovarian failure, loss of ovarian function secondary to castration, infection, hemorrhage or compromised blood supply, and autoimmune oophoritis. The fourth ovarian cause is polycystic ovarian (PCO) disease. Some investigators have stated that PCO disease is due to hypothalamic disorder, but the reason for including it under ovarian causes of amenorrhea is the morphological changes found in the ovaries of patients with the disease.

- *Premature ovarian failure*

This diagnosis is made when ovarian failure occurs at any age between the onset of menarche and age 35. Because the ovaries do not secrete sufficient amounts of estradiol to maintain the negative feedback on the hypothalamus in these patients, the gonadotropins are found to be elevated into the postmenopausal range. Although gonadotropin levels do fluctuate, the levels are consistently elevated and, therefore, a single serum FSH determination is adequate to make the diagnosis. Such patients will not have uterine bleeding following intramuscular administration of progesterone.[37,41] With rare exceptions ovulation cannot be induced with drug therapy and, therefore, these patients should be considered sterile and considered to require estrogen replacement.

- *Loss of the ovarian function secondary to castration, intraovarian infection or interference of blood supply*

Loss of ovarian function following surgical castration is self-explanatory. On rare occasions, patients with severe bilateral tubo-ovarian abscesses have responded well to antibiotic therapy and do not require surgical treatment. In some of these patients the infection completely destroys the ovarian tissue resulting in ovarian failure. Compromise of the ovarian blood supply following hysterectomy may result in cystic degeneration. Usually this process is unilateral and, therefore, amenorrhea does not occur. However, it may occur bilaterally or in the only remaining ovary resulting in loss of ovarian function. These patients are sterile and need estrogen replacement.

- *Autoimmune oophoritis*

Autoimmune endocrine disorders, particularly Hashimoto thyroiditis, are common. These auto-

immune endocrinopathies may affect a single organ or may involve multiple organs. Because in a patient who presents with autoimmune destruction of an endocrine organ, failure of the other glands may develop over the ensuing years, physicians should be continuously observant for the appearance of additional endocrinopathies. The glands affected in the approximate order of occurrence are thyroid, beta cells of the pancreas, adrenals, ovaries, parathyroids, and testes. Ovulation may still occur in a patient with oophoritis if oligomenorrhea is present. Once amenorrhea appears, these patients are infertile and estrogen deficient and should be treated with estrogen replacement therapy.

- *Polycystic ovarian disease*

Patients with PCO disease usually have oligomenorrhea but many have primary or secondary amenorrhea. These patients secrete normal amounts of estradiol and, therefore, have uterine bleeding following intramuscular progesterone administration. It has been reported that 60 percent to 80 percent of patients with PCO disease have elevated serum LH values above 20 mIU per ml and a low normal level of serum FSH. The elevated LH value has been used to differentiate this disorder from patients with hypothalamic dysfunction who have normal levels of serum LH. Although LH does have significant daily fluctuations it has been reported that in patients with PCO disease a single measurement of LH is adequate to make this diagnosis since the fluctuations are usually elevated above the 95 percent confidence limits for normal premenopausal women.

If the patient desires pregnancy, clomiphene citrate is the therapy of choice. If the patient does not desire pregnancy, she should be given cyclic progestin therapy in order to induce uterine bleeding and prevent unopposed estrogen effect on the endometrium which may lead to either benign or atypical hyperplasia. One mode of progestin therapy is to give the patient 10 mg a day of medroxyprogesterone acetate orally for at least five days each month.

Uterine Factors (Uterine Synechiae or the Asherman Syndrome)

Before the above diagnoses can be considered and the appropriate laboratory tests ordered, the uterine factor must be ruled out.[42] The formation of uterine synechiae has usually been associated with dilation and curettage or endometritis. This condition has also been seen following myomectomy and metroplasty and cesarean section. Either total or only partial obliteration of the endometrial cavity may be found. In patients with partial disease, uterine bleeding can be induced with estrogen-progestin therapy. Therefore, this regimen is not always definitive in establishing the diagnosis. Whenever this diagnosis is suggested by history the patient should have an

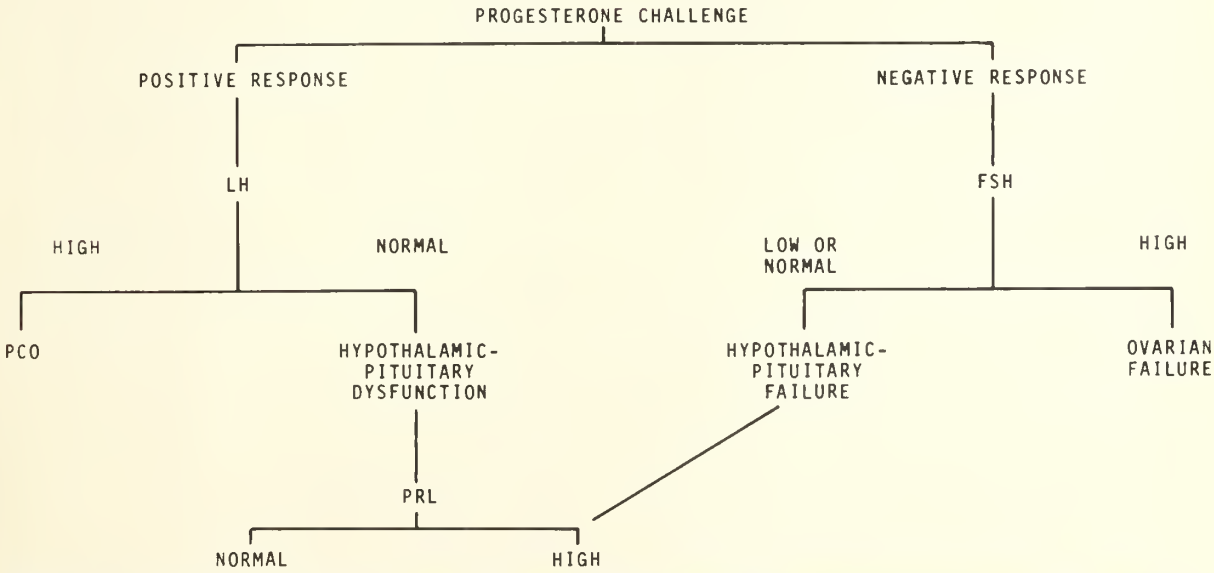

Figure 26.—Scheme for evaluation of patients with secondary amenorrhea without galactorrhea or cortisol or androgen excess. FSH = follicle-stimulating hormone, LH = luteinizing hormone, PCO = polycystic ovarian disease, PRL = prolactin.

evaluation of the uterine cavity by either hysteroscopy or hysterosalpingography. In order to be able to use a simplified approach for the workup of patients with amenorrhea, uterine factors (including pregnancy) must be ruled out.

Evaluation and Therapy

Studies of withdrawal uterine bleeding following an injection of progesterone-in-oil has made it possible to separate cases of amenorrhea into two major categories (Figure 26). In those persons with uterine bleeding a single serum LH value greater than 30 mIU per ml is indicative of polycystic ovarian disease. Normal LH values indicate hypothalamic dysfunction. In these patients a serum prolactin (PRL) determination should be ordered even in the absence of galactorrhea and, if PRL is found to be elevated, polytomographic x-ray studies of the sella turcica should be done to rule out pituitary tumors. If the PRL value is normal, uterine withdrawal bleeding should be induced at least every three months with oral administration of medroxyprogesterone acetate or intramuscular progesterone-in-oil, if the patient does not desire pregnancy. If pregnancy is desired, there should be treatment with clomiphene citrate. As long as patients remain in the dysfunction group it is unnecessary to carry out x-ray studies of the sella turcica, unless they have galactorrhea in addition to the amenorrhea or serum PRL value is elevated. A single serum FSH study (but not an LH determination*) in patients who do not have uterine bleeding can identify two distinct populations. One group will have a low or normal FSH value and the other an elevated value. The group with low or normal FSH levels represents those patients with hypothalamic-pituitary failure while the group with elevated FSH levels represents patients who have ovarian failure.

In all patients with hypothalamic-pituitary failure, a complete pituitary workup should be done to show the presence or absence of a pituitary tumor. This evaluation should include polytomographic evaluation of the sella turcica, visual field examination and computerized axial tomographic (CAT) scans. If no tumor is shown, a PRL determination should be done every six months and x-ray studies of the sella turcica every 24 months. In addition, an insulin-induced hypoglycemia test should be done in all cases to determine the pituitary growth hormone, PRL and ACTH reserve. Because these patients have very low levels of estradiol, they rarely respond to clomiphene citrate. It is recommended that induction of ovulation be first attempted at doses up to 250 mg per day for five days and if they fail to ovulate following this treatment, then therapy with human menopausal gonadotropin (HMG) should be initiated.

Ovarian failure is easily diagnosed because patients with the disorder invariably fail to respond to progesterone challenge and have elevated FSH values. These patients will not respond to any form of ovulatory drug therapy and, therefore, are sterile and should be given estrogen replacement therapy because they do not have adequate endogenous levels of estrogens. The recommended regimen of estrogen replacement is 0.3 or 0.625 mg of conjugated estrogen given on days 1 through 25 of each month. Medroxyprogesterone acetate (Provera), 10 mg administered orally on days 16 through 25, should be given in order to avoid unopposed estrogen effect on the endometrium.

Amenorrheic Patients With Galactorrhea

Galactorrhea can be associated with hypothyroidism, the use of tranquilizers or antihypertensive drugs and prior use of oral contraceptive steroids. Inappropriate lactation has also been reported in patients with Cushing disease, those with acromegaly and those who have had chest trauma. These patients can have normal menstrual cycles or have a hypothalamic-pituitary derangement resulting in oligomenorrhea or amenorrhea. It was hoped that with the development of a sensitive radioimmunoassay for PRL it would be possible to differentiate patients with pituitary tumors from those who have a functional derangement. Unfortunately, this method has not been totally reliable because galactorrheic patients with microadenomas not only can be ovulating but also can have serum PRL levels in the normal range. Therefore, neither the menstrual history nor the PRL level alone can be relied upon to select those patients in whom radiographic evaluation of the sella turcica is required.

The use of tranquilizers poses a significant clinical problem. If a patient can discontinue the use of tranquilizers, the medication should be stopped and a serum PRL level obtained every month until the level drops into the normal range.

*LH is elevated in patients with ovarian failure and low or normal in patients with hypothalamic-pituitary dysfunction. However, values fluctuate widely and a single LH study may not be diagnostic of either catagory.

If in three months after discontinuing the medication, the serum PRL is still elevated, the patient should have a complete evaluation. If the patient cannot function without the use of tranquilizers, and if the level of PRL is above 100 ng per ml, she should be evaluated as outlined below.

A common misconception is that contraceptive steroids taken by mouth may cause galactorrhea. Such contraceptives do not stimulate galactorrhea but in fact may mask the presence of galactorrhea by their suppressive action on the breast. Therefore, if galactorrhea develops in patients taking contraceptive steroids, the medication should be discontinued and the patient evaluated for the presence of a pituitary adenoma. If galactorrhea develops after the use of steroids is discontinued, the complete workup can be delayed for three months. If the galactorrhea is still present at that time a complete evaluation should be started.

In an effort to develop a systematic method for evaluating patients with galactorrhea we recently reported our experience in a series of 149 patients who presented with galactorrhea at our clinic and private service.[43] None were taking tranquilizers or had any clinical evidence of Cushing disease or acromegaly. Galactorrhea was defined as milky or watery breast secretions noted either spontaneously or by expression. The secretion could be unilateral or bilateral. Localized breast disease should be considered in patients with unilateral galactorrhea. Of the 149 patients, three were found to have primary hypothyroidism, an incidence of 2 percent. Because these patients will recover completely following institution of thyroid replacement therapy, a serum TSH determination should be done in a patient with galactorrhea.

If the patient is euthyroid, a serum PRL study should be carried out even if the patient gives a history of having normal menstrual cycles. In six of our series of 32 patients who had normal menses, changes were found on x-ray studies compatible with pituitary microadenomas. All six of these patients did have elevated serum PRL levels. None of the 13 patients who had normal PRL levels were found to have x-ray evidence of

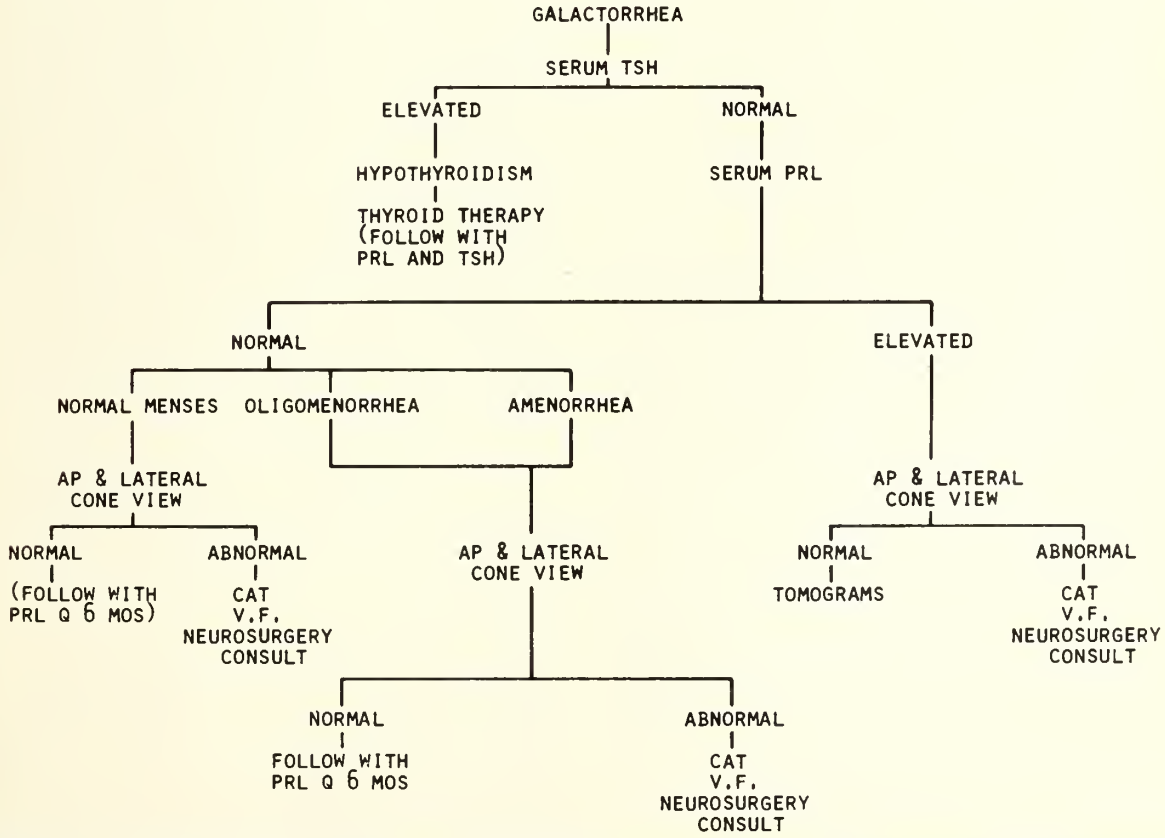

Figure 27.—Schematic outline for the diagnosis and management of patients with galactorrhea. AP = anteroposterior, CAT = computerized axial tomography, PRL = prolactin, TSH = thyroid-stimulating hormone, V.F. = visual field examination.

microadenomas, and, therefore, a low risk category was identified which was comprised of galactorrheic women who were menstruating regularly and had normal PRL levels. In galactorrheic patients who gave a history of either oligomenorrhea or amenorrhea, no such category could be identified because nine patients with normal serum levels of PRL were found to have radiologic evidence compatible with having a pituitary microadenoma. It is clear that galactorrheic patients with amenorrhea, low serum estrogen levels and elevated serum PRL concentrations have a high incidence of pituitary microadenomas. In our series of 42 such patients, 29 (69 percent) had microadenomas.

Utilizing all this information it has been possible to construct an outline for investigating and managing patients with galactorrhea (Figure 27). This approach utilizes a single measurement of serum TSH and PRL in conjunction with the menstrual history and use of polytomograph. The various therapeutic modalities available for treating prolactin-secreting microadenomas or macroadenomas have been discussed recently.[44]

Hirsutism in Adolescents

GLENN D. BRAUNSTEIN, MD*

Normal Hair Growth

HAIR MAY BE CLASSIFIED into three categories: asexual, ambisexual and sexual.[45] Asexual hair, the growth and distribution of which are independent of sex or gonadal steroid production, includes the scalp, eyelash, eyebrow and lumbosacral triangle hair. Ambisexual hair grows in response to low levels of adrenal and gonadal androgens and occurs in both sexes. Thus pubic and axillary hair, hair on limbs and, to a lesser extent, the hair extending along the linea alba from the umbilicus to the pubic triangle fall into this category. Sexual hair is normally restricted to males and is dependent upon the androgen concentration. Beard, moustache, nasal-tip, pinnea, back and chest hair are examples of androgen sensitive sexual hair.[45] Hirsuitism may, therefore, be defined as excessive sexual hair growth in the androgen sensitive areas of the body in a phenotypic female.

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A variety of factors are involved in growth of sexual hair. These include the sensitivity of hair follicles to circulating androgens, the ability of hair follicles to convert weak androgens or androgen precursors to more potent androgens, the potency of the androgens that the hair follicles are exposed to, the location of the hair and the duration of exposure of the follicle to androgens.[46] Sexual hair begins as vellus or fine, lightly pigmented lanugo-type hair which upon exposure to sufficient quantities of androgens may be irreversibly converted to a thick, darkly pigmented, deeply rooted terminal hair. Once a terminal hair is formed it seems that very little androgen is required to maintain hair growth.[47] Terminal sexual hairs go through a growth cycle that varies between two and four years, and at the end of the cycle the hair shaft falls out and new hair formation may take place.[48]

Androgen Metabolism in Women

In a nonpregnant woman, approximately 25 percent of the serum testosterone is derived from direct adrenal secretion, approximately 25 percent from ovarian secretion and 50 percent is derived from peripheral or extraglandular conversion of the 17-ketosteroid androgen precursors, primarily dehydroepiandrosterone (DHEA) (90 percent from adrenal glands, 10 percent from ovaries) and Δ^4-androstenedione (50 percent from adrenal glands, 50 percent from ovaries).[49-51] In addition to testosterone, three other androgens which, like testosterone, are 17β-hydroxysteroids, are important in women. These androgens are Δ^5-androstenediol, dihydrotestosterone and 3 α-androstanediol, and are almost exclusively derived from the extraglandular conversion of DHEA, androstenedione and testosterone.[50] If one takes into account the average plasma concentration of each of these androgens, their relative androgenicity and the amount that exists in the unbound biologically active state in the blood, then an androgenicity index may be computed.[50,52] Therefore, approximately half of the total androgenic activity in the plasma of a normal woman is due to testosterone, while the other three 17β-hydroxysteroids contribute to the remaining androgen activity.

Approximately 99 percent of the circulating androgens are bound to serum proteins, while the remaining 1 percent is unbound and is capable of entering the androgen target tissues to exert its biologic action. The two serum proteins that bind

androgens are testosterone-estradiol-binding globulin (TeBG; sex steroid binding globulin), a protein with high affinity for androgens, and albumin which has a low affinity for androgens but greater binding capacity. The synthesis of TeBG by the liver is increased by estrogen administration, pregnancy and hyperthyroidism, while androgens, some progestogens and glucocorticoids decrease TeBG synthesis.[49-51] Men normally have lower TeBG levels than women and the percent of the androgens that are free is greater in men than women. The TeBG levels in hirsute women are between those found in normal men and women and, therefore, the percentage of unbound androgen is greater than normal.[49-51] This combined with the increased testosterone production rate in hirsute women[49] accounts for the observed increase in the absolute concentration of free testosterone seen in 60 percent to 100 percent of hirsute women.[52-54]

Classification of Hirsutism

Cases of hirsutism may be classified on a clinical basis into those patients with androgen-sensitive excessive hair growth alone and those with associated virilization. Virilization or defeminization includes hirsutism and acne with clinical evidence of a more severe degree of androgenization including malodorous perspiration, deepening of the voice due to enlargement of the larynx (an androgen-sensitive organ), male muscle pattern and body contour development, increased libido, clitoral hypertrophy (greater than 1 cm in diameter) and temporal hair recession. Studies carried out on hirsute and virilized patients have shown that testosterone production rates correlate closely with the clinical manifestations of androgen excess, indicating that hirsutism is on a continuum with virilization.[49] However, for clinical purposes, patients may be divided into those who have simple hirsutism without virilization and and those with hirsutism associated with virilization (Table 4).

Hirsutism Without Virilization

In approximately 99 percent of patients with simple hirsutism there is either no discernible pathologic condition or a benign underlying condition.[55,56] The frequency of hirsutism varies with the population studied. McKnight[57] noted that 9 percent of 440 women students at the University of Wales were hirsute in comparison to their peers, while Ferriman and co-workers[58] found that 10 percent to 15 percent of unselected female patients in hospital and in the 15 to 44 year age range had hirsutism.

The sensitivity of the hair follicles to androgen stimulation is in part under the influence of genetic control. Consequently, daughters of hirsute women have an increased likelihood of being hirsute.[59] In addition to the immediate familial influences, the racial background of the individual person also influences sexual hair growth. Women from the Mediterranean area have more sexual hair on the average than Scandinavian women.[55,60,61] Similarly, Caucasians are more hirsute than Mongoloids.[55] Women with familial or racial hirsutism characteristically note the excessive hair growth beginning around the time of menarche, usually have normal cyclic menses, and generally have normal plasma or serum androgen levels.

Patients without a family history or racial susceptibility for hirsutism and who are not found to have a pathologic problem responsible for their

TABLE 4.—*Causes of Hirsutism in Adolescent Women*

- Without Virilization
  - Normal persons
    - Familial or racial
    - Idiopathic
    - Drugs
    - Pregnancy
  - Pathologic conditions
    - Ovarian disorders
      - Polycystic ovary disease
      - Hyperthecosis
    - Adrenal disorders
      - Bilateral adrenocortical hyperplasia
    - Thyroid disorders
      - Hypothyroidism
    - Pituitary disorders
      - Acromegaly or gigantism
    - Miscellaneous
      - Central nervous system injury
      - ? Emotional stress
      - Malnutrition
      - Porphyria
- With Virilization
  - Normal persons
    - Androgen administration
  - Pathologic conditions
    - Ovarian disorders
      - Polycystic ovary disease
      - Virilizing ovarian tumors
    - Adrenal disorders
      - Congenital adrenal hyperplasia
      - Adrenal carcinoma
      - Virilizing adrenal adenoma
    - Male pseudohermaphroditism

excessive hair growth are classified as having idiopathic hirsutism. Again this disorder begins during the pubertal years with a slowly progessive increase in hair growth during the second and third decades. Menstrual cycles may be normal or abnormal. Those patients with abnormal menstrual cycles generally tend to be more obese and have greater elevations of serum androgens then those with normal cycles.[62] Total serum testosterone is elevated in 33 percent to 82 percent of these patients,[52-54,63-67] while testosterone production rates are increased in over 90 percent.[49] In most instances the ovaries are the source of the excessive androgen production in patients with idiopathic hirsutism.[68]

Pregnancy may be associated with excessive facial, periareolar, intramammary and extremity hair.[69] This is usually noted during the first trimester and may be due to excessive ovarian androgen secretion. This form of hirsutism usually remits antepartum or following delivery.

A number of drugs may cause iatrogenic hirsutism. Diphenylhydantoin may induce hair growth on the trunk, face and extensor surfaces of the extremities, within two to three months after beginning therapy.[70] The increased collagen deposition in the skin and increased cutaneous vascularity may be of etiologic importance. Diazoxide, minoxidil, glucocorticoids, ACTH, anabolic steroids and C-19 progestogens, such as norethindrone and norethynodrel, may be associated with hirsutism.[55] Withdrawal of the offending drug usually results in a disappearance of the excessive hair.

The most frequent pathologic cause of hirsutism without virilization is polycystic ovary disease. Hirsutism occurs in approximately half of the patients with this disorder.[71] These patients may also have obesity, oligomenorrhea or amenorrhea, and involuntary infertility. The hirsutism characteristically begins at the time of puberty and is often slowly progressive. Serum testosterone levels may be normal or elevated, but the testosterone production rate is usually increased.[49] The primary source of the androgens is the ovaries, although combined ovarian and adrenal androgen secretion has been noted.[72] Ovarian hyperthecosis clinically resembles polycystic ovary disease, although the pathologic changes in the ovaries are somewhat different.

Cushing disease with bilateral adrenocortical hyperplasia may be associated with a mild degree of hirsutism, probably due to the combined effects of ACTH-induced adrenal androgen secretion and the reduced levels of TeBG that result from excessive quantities of glucocorticoids.[73] Similarly, reductions in TeBG have been found in patients with hypothyroidism[74] and acromegaly.[75] In each of these disorders hirsutism is not the primary complaint and the other physical stigmata of the underlying endocrinopathy are usually readily apparent.

Although hirsutism is occasionally noted following head injuries, psychogenic stress and disorders associated with starvation such as in anorexia nervosa, the pathophysiologic alterations responsible for the hair growth have not been defined.[71] Hirsutism may occur in the sun exposed areas in patients with porphyria, especially porphyria cutanea tarda.[76] The cause is unclear but may be related to the irritative effects of porphyrin deposition in the skin followed by sunlight exposure.

Hirsutism With Virilization

Hirsutism with virilization is usually due to a significant pathologic disorder. Normal persons given androgens or anabolic steroids may become virilized and some degree of virilization has been noted in approximately 20 percent of the patients with polycystic ovary disease.[77] Rarely, the virilizing forms of congenital adrenal hyperplasia[78] and male pseudohermaphroditism[55] may escape detection until adolescence. Once these conditions are considered and excluded, virilizing ovarian tumors such as arrhenoblastomas, granulosa-theca cell tumors, hilus cell tumors, luteomas of pregnancy, or Krukenberg tumors, and adrenal adenomas or carcinomas are the most likely diagnostic considerations. Both ovarian and adrenal neoplasms present with a rapid onset of hirsutism, menstrual irregularities and virilization because of the secretion of large amounts of androgens or androgen-precursors which are converted to androgens by the peripheral tissues. In addition adrenocortical carcinomas may have signs and symptoms of excessive glucocorticoid and mineralocorticoid production.

Diagnostic Evaluation

In women with simple hirsutism without virilization, a careful family, racial and drug history, and physical examination should be sufficient to allow the diagnosis of familial and drug-induced hypertrichosis, pregnancy, Cushing disease, hypothyroidism, acromegaly, and the miscellaneous

causes of hirsutism. The remaining patients most likely have idiopathic hirsutism or polycystic ovary disease. If menstrual cycles are normal, it is unlikely that the serum androgen levels will be more than minimally elevated. For patients with hirsutism and menstrual irregularities, serum testosterone and luteinizing hormone concentration should be measured. Because of the spontaneous fluctuations in these hormones it is recommended that three blood specimens be obtained 20 minutes apart and the serum separated. Two milliliter aliquots of each of the serums may then be combined and a single testosterone and LH measurement made. This allows integration of the hormone levels in order to obtain a more accurate mean hormone concentration in a cost-effective manner. If testosterone concentrations are less than 200 ng per dl no further evaluation is necessary. Normal or slightly elevated serum testosterone levels with normal LH concentrations are compatable with idiopathic or familial hirsutism, while patients who have elevated testosterone and LH levels are most likely to have polycystic ovary disease.

Patients with a rapid onset of virilization require an intensive endocrinologic evaluation. Serum testosterone and dehydroepiandrosterone-sulfate (DHEA-sulfate) levels should be measured. Pronounced elevation of testosterone with normal DHEA-sulfate concentrations indicates the presence of ovarian neoplasm, while elevated testosterone with high DHEA-sulfate levels is usually indicative of an adrenal disorder. A dexamethasone suppression test should be carried out in the latter patients. In patients with congenital adrenal hyperplasia the serum DHEA-sulfate and testosterone concentrations are suppressed after five days of dexamethasone administration (1 mg given orally twice a day for five days) while in patients with virilizing adrenocortical adenoma or carcinoma this does not occur. Pelvic ultrasound, computerized axial tomographic scans of the adrenals, angiography, or adrenal and ovarian vein catheterization with measurement of androgens in the blood from each organ may be useful for determining the location of ovarian and adrenal neoplasms.

Treatment

If a pathologic condition is found to be responsible for the hirsutism or virilization, therapy directed at the primary disorder should be given because in most instances the hirsutism will regress or the rate of hair growth will diminish. For patients with familial or idiopathic hirsutism or polycystic ovary disease two types of therapy, cosmetic and medical, are available.

The cosmetic therapies include bleaching, plucking, wax stripping, shaving, use of chemical depilatories and electrolysis.[48] Bleaches are most useful for lightly pigmented, shallow terminal hairs in the sideburn or moustache areas. Many women utilize plucking or tweezing of moustache or chin hairs. However, this may lead to local infection of the hair follicle and the repeated skin trauma may actually stimulate vellus hairs to be transformed into terminal hairs.[79] In addition, repeated tweezing may alter the direction of the hair follicle which makes subsequent electrolysis difficult. Wax stripping involves the application of molten wax to the skin. After the wax hardens it is removed and the entrapped hairs are pulled out. Adverse effects of this method of mass plucking include a mechanical and occasional chemical dermatitis, skin infections and increased conversion of vellus to terminal hairs. Shaving does not stimulate the formation of new hairs and does not make hairs coarser or darker.[80] It does cut the hair at the thickest portion of the shaft which may result in a stubble as the hair grows out. Therefore, this treatment should be reserved for excessive thigh, lower extremity, abdominal and periareolar hair. Depilatory creams or pastes chemically shave the hairs off at the skin surface and have the same advantages and disadvantages as shaving.[80]

The only cosmetic therapy that results in permanent removal of hair is electrolysis and its variants.[79] Either electrical or high frequency currents are transmitted through a fine needle which has been inserted along the hair shaft into the hair follicle. This results in desiccation of the hair bulb and papilla. Although this has the advantage of permanently destroying the follicle, only 50 percent to 70 percent of the follicles treated are actually destroyed during any treatment session because of technical difficulties. This form of treatment is expensive, time consuming and painful. If the hirsutism is severe, electrolysis should be combined with some form of medical therapy in order to reduce the rate of new hair growth during treatment.

Several types of medical therapy have been advocated for the treatment of hirsutism. Glucocorticoids, usually given as dexamethasone in doses of 0.5 to 0.75 mg orally at night, decrease

the rate of hair growth in 30 percent to 50 percent of patients.[53,81] These doses will suppress the early morning rise in ACTH and hence adrenal androgen production. In addition there is evidence that ovarian androgen and androgen precursor secretion is diminished by this therapy.[68] The major adverse effects of this therapy are appetite stimulation, weight gain and insomnia. Prolonged suppression of the hypothalamic-pituitary-adrenal axis is usually not seen.[82] Birth control pills containing high concentrations of estrogen, such as Ortho-Novum 2 mg tablets or Norinyl 2 mg tablets, effectively reduce the rate of hair growth in approximately half of the patients.[71,83] These agents decrease ovarian and adrenal androgen production and stimulate the liver to synthesize increased quantities of TeBG.[83,84] Because TeBG is the major serum androgen-binding protein the amounts of free or biologically active androgens are reduced. It should be noted that the major adverse effects attributed to birth control pills are due to the estrogen content and, therefore, both physicians and patients must carefully weigh the potential risks of using these agents for treating a cosmetic problem.

Several experimental therapies for hirsutism have been developed. Medroxyprogesterone acetate in a dose of 100 mg given intramuscularly every two weeks or 30 to 40 mg given orally daily has been shown to reduce serum androgen levels by decreasing testosterone production.[85,86] This agent may also interfere with the peripheral action of the androgens at the androgen target organ level.[86] Breakthrough bleeding, menstrual irregularities and increased appetite with weight gain may occur. Spironolactone displaces androgens from their intracelluar binding protein and has recently been shown to reduce excessive hair growth in hirsute women.[87] Another antiandrogen, which has been used extensively in Europe but is not available in the United States, is cyproterone acetate. Like spironolactone, this drug displaces androgens from the receptor proteins in androgen-sensitive tissues. It is 60 percent to 80 percent effective in reducing hair growth but should be given cyclically with estrogens because of the frequently associated menstrual abnormalities.[88,89]

Because of the long (two to four year) cycle of hair growth in the androgen-sensitive areas of the body, patients should be told that at least six months of therapy may be required before a sufficient number of hairs are lost to allow an objective assessment of the therapeutic effects. In addition patients should not be told that the excessive hair will disappear. Rather, it should be emphasized that effective medical therapy will only reduce the rate of hair growth, which when combined with the cosmetic therapies may lead to an acceptable psychosocial result.

The Clinical Consequences of Stilbestrol Exposure *In Utero*

ROBERT J. KURMAN, MD*

IN 1971 HERBST and associates[90] described the cases of eight young women with clear cell carcinoma of the vagina exposed to diethylstilbestrol (DES) *in utero*. A Registry of Clear-Cell Adenocarcinoma of the Genital Tract in Young Women (now the Registry for Research on Hormonal Transplacental Carcinogenesis) was established to centralize data on these patients thereby facilitating rapid dissemination of information on the biological behavior of these tumors and on appropriate therapeutic modalities. At present, the Registry serves as a repository for clinical and pathologic data on more than 330 women with this neoplasm. Reports from the Registry[91,92] and additional publications from other institutions[93-106] have not only substantiated the association of vaginal and cervical clear cell carcinoma with *in utero* DES exposure, but have also shed light on a group of benign lesions resulting in pronounced alterations of the lower genital tract. These alterations include cervical or vaginal ridges and ectopic location of benign glandular epithelium in the vagina (adenosis) and cervix (ectropion).[103-106] There have also been reports suggesting that due to the presence of extensive vaginal adenosis and cervical ectropion in these patients, there may be an increased risk of squamous carcinoma of the vagina and cervix.[107,108] These findings have widespread implications; it has been estimated that several hundred thousand young women were exposed to DES *in utero* between 1945 and 1970 in the United States[109] when DES was used to treat patients with threatened and repeated abortions. This form of therapy was used not only in the

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United States but throughout other countries in Europe, South America, Africa and Australia.

Epidemiologic and Clinical Features

Review of almost 300 cases of clear cell carcinoma from the Registry files indicates that in almost two thirds of the patients there is a history of maternal DES or chemically related nonsteroidal estrogen such as dienestrol or hexestrol (Table 5). Patients without a history of *in utero* DES exposure most often represent those in whom medical records were incomplete.[91,92] In some women with no history of exposure the tumor may have arisen spontaneously since neoplasms of this variety, especially in the cervix, were rarely reported before the DES era.[110,111] The doses of hormone administered during pregnancy varied from 1.5 to 150 mg per day. In all instances, therapy was initiated in the first half of pregnancy corresponding to the stage of embryogenesis during which the female genital tract develops.[112]

There are eight cases in the Registry files with a history of exposure to non-DES hormones including steroidal estrogens and progesterone, but these are regarded as sporadic cases, a causal relationship between the neoplasm and the steroid hormones having not been shown to exist.[112]

TABLE 5.—*Maternal Medication in Pregnancy (284 patients)*

Pregnancy Rx	*Number of Patients*	*Percent*
DES, dienestrol, hexestrol	182	64
No history of medication	75	26
Unknown medication for bleeding	27	10
TOTAL	284	100

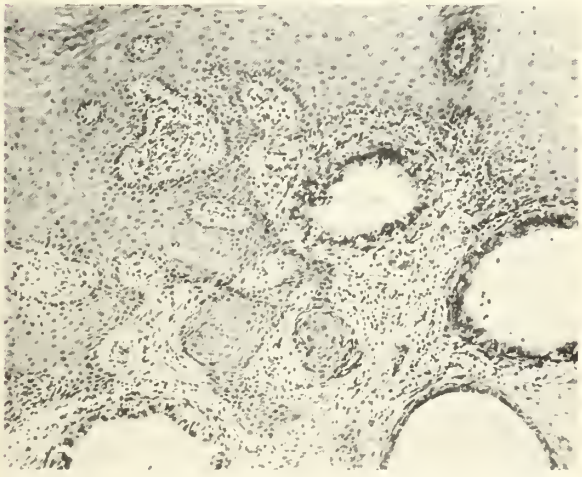

Figure 28.—Vaginal adenosis characterized by glands lying immediately beneath surface squamous epithelium. (Hematoxylin-eosin stain, reduced from 120×.)

The patients with carcinoma range in age from 7 to 29 years and the mean latency period from the time of exposure to the initial diagnosis of carcinoma is 19 years. Most of the tumors appear from 14 to 23 years of age.

A determination of the risk factor for an exposed person is imprecise because the exact number of women exposed to DES is unknown. Based on data from medical centers in which DES was used in the early 1950's, it appears that probably in fewer than one woman out of a thousand exposed will the tumor develop in adolescence.[112]

Benign Lesions Associated With DES Exposure

Although the clear cell carcinoma has received the widest attention, it is a relatively infrequent sequela of maternal DES treatment. In contrast, almost all women exposed to DES will have one or more of the benign conditions which include vaginal adenosis, cervical ectropion, and gross vaginal and cervical deformities. The terms cervical pseudopolyp,[103,113] strawberry cervix,[104] cervical cock's comb-like lesion,[104,106] erythroplakia,[104] vaginal pericervical collar,[103] vaginal hood[104,106] and vaginal band[93] have been used to describe these changes, but they are all variants of the three basic lesions.

Adenosis is defined as the presence of benign glandular epithelium in the vagina, either in the form of glands lying beneath the vaginal mucosa (Figure 28) or replacing the surface epithelium.[103] Cervical ectropion is defined as glandular epithelium on the exocervix. Although adenosis has been reported in patients in the absence of antenatal DES exposure,[114,115] clinically detectable adenosis is almost always confined to women exposed to DES *in utero*. Adenosis in these patients is most often located on the anterior upper part of the vagina (in fact, confined to this area in almost 90 percent of cases[116]) in continuity with cervical ectropion. The natural history of both vaginal adenosis and the cervical ectropion is similar resulting in replacement of the glandular epithelium by squamous epithelium (Figure 29). This metaplastic squamous epithelium is at first immature but then differentiates into mature squamous epithelium and becomes glycogenated. Ultimately, it is indistinguishable from the mature squamous epithelium lining the vagina and exocervix. The zone of active squamous metaplasia

intermingled with columnar glandular epithelium (adenosis and ectropion) is analogous to the process observed on the cervix of virtually all women and is referred to by colposcopists as the transformation zone.

It is believed by some that one of the basic abnormalities of DES exposure is an extension of the transformation zone from the cervix to the vagina.[108] Because dysplasia and the squamous carcinoma of the cervix arise in the transformation zone, the presence of a large transformation zone covering the cervix and upper vagina in DES exposed women has led some colposcopists to speculate that there will be an increase in the incidence of squamous carcinoma in these women.[107,108] Recent evidence, however, does not support this hypothesis. Although long-term follow-up is still necessary, a study in which 1,400 DES-exposed women were examined showed that the prevalence of vaginal and cervical dysplasia was 2.1 percent over a follow-up period of five years. The dysplastic changes were almost always mild, whereas severe dysplasia and carcinoma *in situ* were never encountered.[117] Studies utilizing nuclear DNA microspectrophotometry technique on biopsy specimens after a diagnosis of severe dysplasia or carcinoma *in situ* have shown that an aneuploid distribution of nuclear DNA, consistent with intraepithelial neoplasia, is found in only a small percentage of these cases. The authors conclude that there is an appreciable rate of misinterpretation of squamous lesions occurring in female DES-exposed patients.[118] This is not surprising since squamous metaplasia found in association with adenosis is often active and immature and when it replaces all the glands of adenosis may, on superficial inspection, even simulate invasive squamous carcinoma.

Figure 29.—Metaplastic squamous epithelium replacing mucinous epithelium of vaginal adenosis. (Hematoxylin-eosin stain, reduced from 490×.)

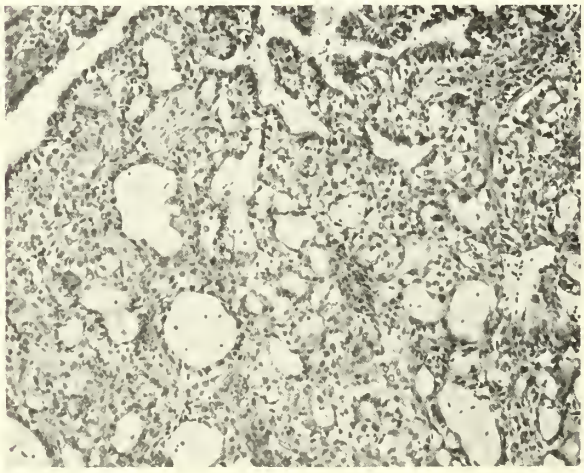

Figure 30.—Microglandular hyperplasia arising in vaginal adenosis characterized by densely crowded glands. The epithelium lining the glands is comprised of one layer with uniform benign appearing nuclei. (Hematoxylin-eosin stain, reduced from 100×.)

Another benign lesion arising in vaginal adenosis has been termed microglandular hyperplasia and occurs in patients using birth control pills. This is analogous to microglandular hyperplasia of the cervix (pill polyp) occasionally observed in women not exposed to DES but taking birth control pills; it has been confused both clinically and pathologically with adenocarcinoma.[119] The histologic features are distinctive (Figure 30) and the lesion is benign requiring no further treatment after biopsy.

Structural disorders such as cervical and vaginal ridges and septae occur in 22 percent to 58 percent of the exposed patients.[103,105,120] These generally have little clinical consequence except that their recognition should alert gynecologists to the possibility of DES exposure. Sometimes a septum must be excised to permit adequate visualization of the cervix and vagina at the time of examination. Another complication resulting from the gross structural abnormalities of the lower genital tract is the occurrence of an incompetent cervix in pregnant patients.[121]

Thus far lesions involving the upper genital tract and ovaries have been limited to the uterine cavity which have been discovered by the use of hysterosalpingograms. These abnormalities include a T-shaped uterine cavity, uterine synechiae and hypoplasia in 60 percent of the patients.[122]

Recent findings indicate alterations detected in exposed males have been epididymal cysts, hy-

poplastic testes, cryptorchidism and abnormalities of sperm including decreased counts, abnormal forms and decreased motility.[123]

Clear Cell Adenocarcinoma

Based on the predominant location of the tumor the ratio of vaginal to cervical tumors is 7:3. The vaginal tumors are usually located in the upper third of the vagina or the anterior wall while the cervical tumors are almost always on the exocervix.[91,92]

The vaginal and cervical tumors are similar in gross appearance, most being polypoid, nodular or papillary but some flat or ulcerated. Microscopically the tumors display solid, papillary, tubular and cystic patterns and are comprised of clear cells containing abundant glycogen (Figure 31), hobnail cells characterized by scant cytoplasm and a large nucleus protruding into a lumen (Figure 32) and flattened cells. When the tumor consists predominantly of cysts lined by flattened epithelium it may have an innocuous appearance.[91,92] The identical tumor can occur in the endometrium[124,125] and ovary[126,127] but in these sites there has never been an association with DES exposure and the neoplasms occur in older, generally postmenopausal women.

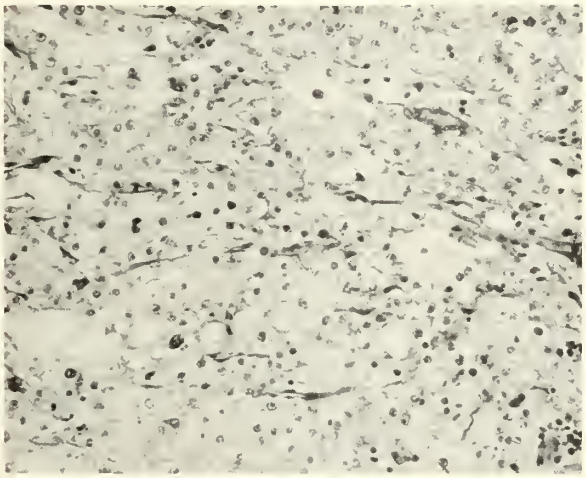

Figure 31.—Clear cell carcinoma characterized by a solid sheet of clear cells. (Hematoxylin-eosin stain, reduced from 150×.)

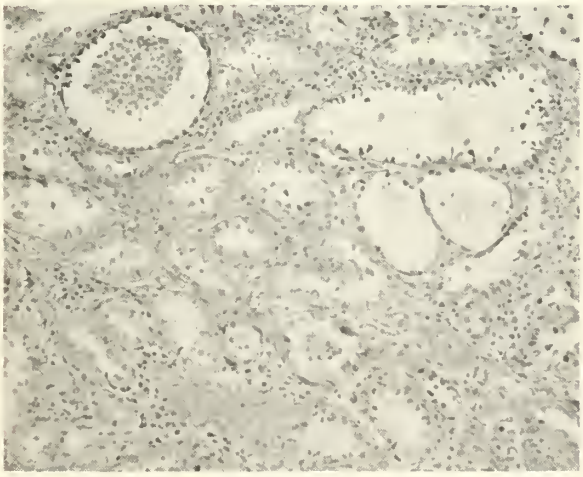

Figure 32.—Tubules within tumor lined by hobnail-shaped cells. (Hematoxylin-eosin stain, reduced from 170×.)

The tumors spread by local extension, and blood vessel and lymphatic metastasis. Approximately 17 percent of patients with stage I tumors of the cervix and vagina have pelvic lymph node metastasis when first seen.[92] Clear cell carcinoma has a greater propensity for distant metastasis than squamous carcinoma originating in the same sites. Approximately 35 percent of recurrent clear cell carcinoma involves the lungs and supraclavicular lymph nodes compared with only 5 percent to 10 percent of recurrent squamous carcinoma.[128]

Factors related to survival include stage, size and depth of invasion of the primary tumor and to a lesser extent, histologic pattern, mitotic activity and grade. It should be emphasized, however, that although size is an important prognostic feature, pelvic lymph node metastasis has been reported with a tumor as small as 2 by 2 mm[129] and with a depth of invasion of 1.5 mm.[92]

Pathogenesis of DES-Related Lesions

The statistically significant association of adenosis and gross structural abnormalities of the lower genital tract in DES exposed women, at a time when the vagina and cervix are developing, provides convincing evidence that DES acts as a teratogenic agent leading to abnormal vaginal development.

The vagina develops from a solid core of tissue referred to as the vaginal plate. This structure is located at a point where the lower fused portion of the müllerian ducts penetrates the urogenital sinus. The epithelium of the vaginal plate extends cephalad replacing that of the fused müllerian ducts and subsequently canalizes; the entire process is completed by the fifth month of gestation.[130-133] It appears that DES interferes with the replacement of the glandular müllerian epithelium by the squamous epithelium derived from the vaginal plate. The administration of estrogens has been shown to inhibit the replacement of the müllerian epithelium, thereby resulting in the

aberrant location of glandular epithelium in the vagina and cervix.[134] Gland-like downgrowths into the stroma of the vagina of neonatal mice have also been produced by the administration of estradiol-17β and DES.[135] Since it has been shown in these animals that the underlying stroma can induce epithelial changes in the vagina[136] it is conceivable that DES may have its primary effect on this stroma, therefore also accounting for the various gross structural abnormalities observed.

The precise role of DES as a carcinogen is not as clear as the action of DES as a teratogenic agent. Clear cell carcinoma, being an adenocarcinoma, must arise from glandular tissue. Since the vagina is normally devoid of glands and adenosis is present closely admixed with the tumor in 95 percent of cases, it is generally accepted that the clear cell carcinoma arises from adenosis. Nonetheless, despite the common occurrence of adenosis in the exposed population, the development of carcinoma is quite rare. Furthermore, the tumors appear to develop over a comparatively brief interval, the incidence rising sharply from age 14 to a peak of 19 years and then declining through age 22. This is unusual because most tumors, even those occurring after a long latent period, develop over a wide age range. This indicates that other factors may play a role in initiating the neoplastic process. The sharp rise in incidence at age 14 corresponding with the onset of puberty suggests that hormonal stimulation may play a role. DES, therefore, may act primarily as a teratogenic agent leading to the formation of adenosis which is a necessary precursor for the development of clear cell carcinoma. Stimuli which do not affect the native squamous epithelium of the vagina may be capable of inducing a neoplastic change in glandular tissue normally not present in this location.

Clinical Evaluation of DES Exposed Women

All women exposed to antenatal DES must be examined starting either at the time of menarche or by the age of 14 years if this has not occurred. Examination should include visualization of the entire circumference and length of the vagina and cervix supplemented by iodine staining and colposcopy. The latter may be confusing, however, since the extensive immature squamous metaplasia which occurs in these patients makes interpretation difficult. In view of the lack of correlation between the colposcopic and the histologic findings[137] it is felt by some colposcopists that this technique is best utilized to assess the extent of the epithelial change rather than as a means for directing biopsies.[138]

TABLE 6.—*Survival After Therapy (297 patients)*

Location and Stage	*Number of Patients*	*Number Alive*	*Number with Recurrence*	*Number Dead*	*Percent Living Free of Disease*
Vagina					
Stage I	129	103	16	10	80
Stage II	36	28	2	6	17
Stages III and IV	11	0	2	9	0
Subtotal	176	131	20	25	
(Percent)	(100)	(75)	(11)	(14)	
Cervix					
Stage I	46	41	1	4	90
Stage IIA	43	30	6	7	70
Stage IIB	20	11	0	9	55
Stages III and IV	12	2	2	8	17
Subtotal	121	84	9	28	
(Percent)	(100)	(70)	(7)	(23)	
TOTAL	297	215	29	53	
(Percent)	(100)	(73)	(9)	(18)	

Another vital aspect of the examination is palpation. Small tumors have been initially detected by palpating areas of induration that may be extremely difficult to visualize.

Cytologic examination is an important screening technique despite the fact that positive or suspicious smears have been reported in only 76 percent of patients with tumors.[139] The percentage cited in this particular study, which was based on data in the Registry files, probably represents inadequate sampling. It has been shown more recently that with thorough collection techniques utilizing four quadrant scrapings of the entire length of the vagina, adenosis can be detected in the majority of patients, corresponding closely with adenosis detected by colposcopy.[140] Thus, cytology is useful as a screening technique if carefully employed.[141,142]

Biopsy specimens should be taken from areas that feel indurated or cystic, from discrete lesions that appear red, granular or ulcerated, and from areas with highly abnormal colposcopic patterns—that is, atypical vessels or heavy mosaic and punctation.[138] Depending on the findings at the initial examination, follow-up should be at 6 to 12 month intervals.

Treatment and Survival

Approximately a fourth of 297 young women with clear cell carcinoma of the vagina and cervix whose cases were followed have either died or

recurrent tumors have developed. This figure must still be regarded as tentative, however, in view of the relatively short follow-up period[92] (Table 6). In two patients recurrence has developed after a seven year disease-free interval, emphasizing the need for prolonged follow-up.[112]

Both radical surgical procedures and radiation have been used effectively for patients with stage I vaginal tumors and stage I and IIa cervical lesions.[92] Local resection has been advocated by some[142] for small superficial lesions; however, 17 percent of patients with stage I tumors of the cervix and vagina have pelvic lymph node metastasis and lymph node metastasis has occurred with tumors that have invaded only 1.5 mm.[92] At present, therefore, wide local excision cannot be recommended.

Local pelvic recurrence has been successfully controlled with both surgical operation and radiation but the results with chemotherapy have been disappointing. Multiple chemotherapeutic agents are being advocated for control of disseminated disease. These include cyclophosphamide (Cytoxan), vincristine, 5-fluorouracil, methotrexate and prednisone.[112]

REFERENCES

1-36, see Part I, Nov 1979 issue.

37. Kletzky OA, Davajan V, Nakamura RM, et al: Clinical categorization of patients with secondary amenorrhea using progesterone-induced uterine bleeding and measurement of serum gonadotropin levels. Am J Obstet Gynecol 121:695-703, Mar 1975

38. Mishell DR Jr, Kletzky OA, Brenner PF, et al: The effect of contraceptive steroids on hypothalamic-pituitary function. Am J Obstet Gynecol 128:60-74, May 1979

39. Kletzky AO, Nicoloff J, Davajan V, et al: Idiopathic hypogonadotrophic hypogonadal primary amenorrhea. J Clin Endocrinol Metab 43:893-900, Oct 1976

40. Vikersky RA, Andersen AE, Thompson RH, et al: Hypothalamic dysfunction in secondary amenorrhea associated with simple weight loss. N Engl J Med 297:1141-1145, Nov 1977

41. Kletzky OA, Davajan V, Nakamura RM, et al: Classification of secondary amenorrhea based on distinct hormonal patterns. J Clin Endocrinol Metab 41:660-668, Oct 1975

42. Toaff R, Ballas S: Traumatic hypomenorrhea-amenorrhea (Asherman's syndrome). Fert Steril 30:379-387, Oct 1978

43. Davajan V, Kletzky OA, March CM, et al: Significance of galactorrhea on patients with normal menses, oligomenorrhea and secondary amenorrhea. Am J Obstet Gynecol 130:894-900 Apr 1978

44. Reichlin S: The prolactinoma problem. N Engl J Med 300: 313-315, Feb 1979

45. Garn SM: Types and distribution of the hair in man. Ann N Y Acad Sci 53:498-507, Mar 1951

46. Muller SA: Hirsutism: A review of the genetic and experimental aspects. J Invest Dermat 60:457-474, Jun 1973

47. Strong JA, Bruce J, Falconer CWA: Hirsutism after adrenalectomy. Lancet 2:1055-1056, Dec 1959

48. Bethune JE: Treatment of hirsutism, virilism and complications of adrenal steroid therapy. Mod Treat 3:1405-1420, Nov 1966

49. Kirschner MA, Bardin CW: Androgen production and metabolism in normal and virilized women. Metabolism 21:667-688, Jul 1972

50. Rosenfield RL: Relationship of androgens to female hirsutism and infertility. J Reprod Med 11:87-95, Sep 1973

51. Givens JR: Normal and abnormal androgen metabolism. Clin Obstet Gynecol 21:115-123, Mar 1978

52. Rosenfield RL: Plasma testosterone binding globulin and indexes of the concentration of unbound plasma androgens in normal and hirsute subjects. J Clin Endocrinol Metab 32:717-728, Jun 1971

53. Paulson JD, Keller DW, Wiest WG, et al: Free testosterone concentration in serum: Elevation is the hallmark of hirsutism. Am J Obstet Gynecol 128:851-857, Aug 1977

54. Tulchinsky D, Chopra IJ: Estrogen-androgen imbalance in patients with hirsutism and amenorrhea. J Clin Endocrinol Metab 39:164-169, Jul 1974

55. Muller SA: Hirsutism. Am J Med 46:803-817, May 1969

56. Coulam CB: The hirsute person: A commentary. Med Clin N Am 58:877-884, Jul 1974

57. McKnight E: The prevalence of hirsutism in young women. Lancet 1:410-413, Feb 1964

58. Ferriman D, Thomas PK, Purdie AW: Constitutional virilism. Br Med J 2:1410-1412, Dec 1957

59. Lorenzo EM: Familial study of hirsutism. J Clin Endocrinol Metab 31:556-564, Nov 1970

60. Danforth CM, Trotter M: The distribution of body hair in white subjects. Am J Phys Anthrop 5:259-265, Mar 1922

61. Hamilton JB, Terada H: Interdependence of genetic, aging, and endocrine factors in hirsutism, *In* Greenblatt R (Ed): The Hirsute Female. Springfield, IL, Charles C Thomas, 1963, p 20

62. Zorn EM, Wieland RG, Hallberg MC: 17β-ol androgens and free index in hirsute and hirsute obese women. Fert Steril 27: 916-920, Aug 1976

63. Aakuaag A, Vogt JH, Fylling P: Plasma and urinary androgens in hirsute women during adrenal and ovarian suppression. Acta Endocrinol 64:103-110, May 1970

64. Ettinger B, Von Werder K, Thenaers GC, et al: Plasma testosterone stimulation: Suppression dynamics in hirsute women. Am J Med 51:170-175, Aug 1971

65. Abraham GE, Chakmakjian ZH: Plasma steroids in hirsutism. Obstet Gynecol 44:171-175, Aug 1974

66. Judd HL, McPherson RA, Rakoff JE, et al: Correlation of the effects of dexamethasone administration on urinary 17-ketosteroid and serum androgen levels in patients with hirsutism. Am J Obstet Gynecol 128:408-417, Jun 1977

67. Bardin CW, Lipsett MB: Testosterone and androstenedione blood production rates in normal women and women with idiopathic hirsutism or polycystic ovaries. J Clin Invest 46:891-902, May 1967

68. Kirschner MA, Zucker IR, Jespersen D: Idiopathic hirsutism—An ovarian abnormality. N Engl J Med 294:637-640, Mar 1976

69. Stoddard FJ: Hirsutism in pregnancy. Am J Obstet Gynecol 49:417-422, Mar 1945

70. Livingston S, Petersen D, Boks LL: Hypertrichosis occurring in association with Dilantin therapy. J Pediatr 47:351-352, Sep 1955

71. Leng J-J, Greenblatt RB: Hirsutism in adolescent girls. Pediatr Clin North Am 19:681-703, Aug 1972

72. Kirschner MA, Jacobs JB: Combined ovarian and adrenal vein catheterization to determine the site(s) of androgen overproduction in hirsute women. J Clin Endocrinol Metab 33:199-209, Aug 1971

73. Vermeulen A, Verdonch L, Vander Straeten M, et al: Capacity of the testosterone-binding globulin in human plasma and influence of specific binding of testosterone on its metabolic clearance rate. J Clin Endocrinol Metab 29:1470-1480, Nov 1969

74. Anderson DC: Sex-hormone-binding globulin. Clin Endocrinol (Oxf) 3:69-96, Jan 1974

75. DeMoor P, Heyns W, Bouillon R: Growth hormone and the steroid binding β-globulin of human plasma. J Steroid Biochem 3:593-600, Apr 1972

76. Zeligman I: Patterns of porphyria in the American Negro. Arch Dermat 88:616-626, Nov 1963

77. Goldzieher JW, Axelrod LR: Clinical and biochemical features of polycystic ovarian syndrome. Fertil Steril 14:631-653, Nov-Dec 1963

78. Faglia G, Trauaglini R, Neri V, et al: Occurrence of a virilizing syndrome with 21-hydroxylase deficiency after pregnancy. J Clin Endocrinol Metab 29:1325-1329, Oct 1969

79. Chernosky ME: Permanent removal of superfluous hair. Texas Med 67:72-78, Oct 1971

80. Peereboom-Wynia JDR: Effect of various methods of depilation on density of hairgrowth in women with idiopathic hirsutism. Arch Derm Forsch 243:164-176, Aug 1972

81. Ettinger B, Goldfield EB, Burrill KC, et al: Plasma testosterone dynamics in hirsute women—Correlation with long-term therapy. Am J Med 54:195-200, Feb 1973

82. Boyers SP, Abramham GE: Recovery of pituitary-adrenal function in hirsute women following chronic low-dose dexamethasone suppression. Abstracts of the 26th Annual Meeting of the Pacific Coast Fertility Society, Oct 18-22, 1978 (Abstract 21)

83. Givens JR, Andersen RN, Wiser WL, et al: The effectiveness of two oral contraceptives in suppressing plasma androstenedione, testosterone, LH, and FSH, and in stimulating plasma testosterone-binding capacity in hirsute women. Am J Obstet Gynecol 124:333-339, Feb 1976

84. Beck RP, Moreos F, Fawcett D, et al: Adrenocortical function studies during the normal menstrual cycle and in women receiving norethindrone with and without mestranol. Am J Obstet Gynecol 112:364-368, Feb 1972

85. Correa de Oliveira RF, Novaes LP, Lima MB, et al: A new treatment for hirsutism. Ann Intern Med 83:817-819, Dec 1975

86. Ettinger B, Golditch IM: Medroxyprogesterone acetate for the evaluation of hypertestosteronism in hirsute women. Fert Steril 28:1285-1288, Dec 1977

87. Boisselle A, Tremblay RR: Clinical usefulness of spironolactone in the treatment of acne and hirsuitism. Clin Res 26:840A, Dec 1978

88. Hammerstein J, Meckles J, Leo-Rossberg I, et al: Use of cyproterone acetate (CPA) in the treatment of acne, hirsutism and virilism. J Steroid Biochem 6:827-836, Jun 1975

89. Dewhurst CJ, Underhill R, Goldman S, et al: The treatment of hirsutism with cyproterone acetate (an anti-androgen). Br J Obstet Gynaecol 84:119-213, Feb 1977

90. Herbst AL, Ulfelder H, Poskanzer DC: Adenocarcinoma of the vagina: Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med 284:878-881, Apr 1971

91. Herbst AL, Kurman RJ, Scully RE, et al: Clear-cell adenocarcinoma of the genital tract in young females—Registry Report. N Engl J Med 287:1259-1264, Dec 1972

92. Herbst AL, Robboy SJ, Scully RE, et al: Clear-cell adenocarcinoma of the vagina and cervix in girls: Analysis of 170 Registry cases. Am J Obstet Gynecol 119:713-724, Jul 1974

93. Barber HRK, Sommers SC: Vaginal adenosis, dysplasia, and clear-cell adenocarcinoma after diethylstilbestrol treatment in pregnancy. Obstet Gynecol 43:645-682, May 1974

94. Fetherston WC, Meyers A, Speckhard ME: Adenocarcinoma of the vagina in young women. Wis Med J 71:87-93, Feb 1972

95. Greenwald P, Barlow JJ, Nasca PC, et al: Vaginal cancer after maternal treatment with synthetic estrogens. N Engl J Med 285:390-392, Aug 1971

96. Hill EC: Clear-cell carcinoma of the cervix and vagina in young women—A report of six cases with association of maternal stilbestrol therapy and adenosis of the vagina. Am J Obstet Gynecol 116:470-484, Jul 1973

97. Kantor HL, Weinstein SA, Kaye HL: Clear-cell adenocarcinoma in young women. Obstet Gynecol 41:443-446, Mar 1972

98. Noller KL, Decker DG, Lanier AP, et al: Clear-cell adenocarcinoma of the cervix after maternal treatment with synthetic estrogens. May Clin Proc 47:629-630, Sep 1972

99. Nordquist SRB, Fidler WJ Jr, Woodruff JM, et al: Clear-cell adenocarcinoma of the cervix and vagina—A clinicopathologic study of 21 cases with and without a history of maternal ingestion of estrogens. Cancer 37:858-871, Feb 1976

100. Roth LM, Hornback NB: Clear-cell adenocarcinoma of the cervix in young women. Cancer 34:1761-1768, Nov 1974

101. Silverberg SG, DeGiorgi LS: Clear-cell carcinoma of the vagina: A clinical, pathologic, and electron microscopic study. Cancer 29:1680-1690, Jun 1972

102. Tsukada Y, Hewett WJ, Barlow JJ, et al: Clear-cell adenocarcinoma ("mesonephroma") of the vagina: Three cases associated with maternal synthetic nonsteroid estrogen therapy. Cancer 29:1208-1214, May 1972

103. Herbst AL, Kurman RJ, Scully RE: Vaginal and cervical abnormalities after exposure to stilbestrol in utero. Obstet Gynecol 40:287-298, Sep 1972

104. Pomerance W: Post-stilbestrol secondary syndrome. Obstet Gynecol 42:12-18, Jul 1973

105. Sandberg EC: Benign cervical and vaginal changes associated with exposure to stilbestrol in utero. Am J Obstet Gynecol 125:777-788, Jul 1976

106. Stafl A, Mattingly RF, Foley DV, et al: Clinical diagnosis of vaginal adenosis. Obstet Gynecol 43:118-128, Jan 1974

107. Fetherston WC: Squamous neoplasia of vagina related to DES syndrome. Am J Obstet Gynecol 122:176-180, May 1975

108. Stafl A, Mattingly RF: Vaginal adenosis: A pre-cancerous lesion? Am J Obstet Gynecol 120:666-673, Nov 1974

109. Heinonen OP: Diethylstilbestrol in pregnancy—Frequency of exposure and usage patterns. Cancer 31:573-577, Mar 1973

110. Hameed K: Clear-cell "mesonephric" carcinoma of the uterine cervix. Obstet Gynecol 32:564-575, Oct 1968

111. Studdiford WE: Vaginal lesions of adenomatous origin. Am J Obstet Gynecol 73:641-656, Mar 1957

112. Herbst AL, Cole P: Epidemiological and clinical aspects of clear-cell adenocarcinoma in young women, chap 11, *In* Herbst AL (Ed): Proceedings of Symposium on DES, 1977, The American College of Obstetricians and Gynecologists, 1978, pp 2-7

113. Shane JM, Perlmutter JR: Pseudopolyp of the uterine cervix. Am J Obstet Gynecol 115:273-274, Jan 1973

114. Kurman RJ, Scully RE: The incidence and histogenesis of vaginal adenosis. Human Path 5:265-276, May 1974

115. Sandberg EC, Danielson RE, Cauwet RW, et al: Adenosis vaginae. Am J Obstet Gynecol 93:209-222, Sep 1965

116. Ng AB, Reagen JW, Nadji M, et al: Natural history of vaginal adenosis in women exposed to diethylstilbestrol in utero. J Reprod Med 18:1-13, Jan 1977

117. Robboy SR, Keh PC, Nickerson RJ, et al: Squamous cell dysplasia and carcinoma in situ of the cervix and vagina after prenatal exposure to diethylstilbestrol. Obstet Gynecol 51:528-535, May 1978

118. Richart RM, Fu YS, Reagen JW, et al: The problem of squamous neoplasia in female DES progeny, *In* Herbst AL (Ed): Intrauterine Exposure of Diethylstilbestrol in the Human. Chicago, The American College of Obstetricians and Gynecologists 1978, pp 45-52

119. Robboy SR, Welch WR: Microglandular hyperplasia in vaginal adenosis associated with oral contraceptives and prenatal diethylstilbestrol exposure. Obstet Gynecol 49:430-434, Apr 1977

120. Herbst AL, Poskanzer DC, Robboy SJ, et al: Prenatal exposure to stilbestrol—A prospective comparison of exposed female offspring with unexposed controls. N Engl J Med 292: 334-339, Feb 1975

121. Singer MS, Hochman M: Incompetent cervix in a hormone-exposed offspring. Obstet Gynecol 51:625-626, May 1978

122. Kaufman RH, Binder GL, Gray PM Jr, et al: Upper genital tract changes associated with exposure in utero to diethylstilbestrol. Am J Obstet Gynecol 128:51-56, May 1977

123. Gill WB, Schumacher GFB, Bibbo M: Structural and functional abnormalities in the sex organs of male offspring of mothers treated with diethylstilbestrol (DES). J Reprod Med 16:147-152, Apr 1976

124. Kurman RJ, Scully RE: Clear-cell carcinoma of the endometrium—An analysis of 21 cases. Cancer 37:872-882, Feb 1976

125. Silverberg SG, DeGiorgi LS: Clear-cell carcinoma of the endometrium—Clinical pathologic and ultrastructural findings. Cancer 31:1127-1140, May 1973

126. Kurman RJ, Craig JM: Endometrioid and clear-cell carcinoma of the ovary. Cancer 29:1653-1664, Jun 1972

127. Norris HJ, Robinowitz M: Ovarian adenocarcinoma of mesonephric type. Cancer 28:1074-1081, Oct 1971

128. Robboy SJ, Herbst AL, Scully RE: Clear-cell adenocarcinoma of the vagina and cervix in young females: Analysis of 37 tumors that persisted or recurred after primary therapy. Cancer 34:606-614, Sep 1974

129. Chambers J, Rogers LW, Julian CG: Minute clear-cell carcinoma of the vagina with early metastasis to pelvic lymph nodes. Am J Obstet Gynecol 131:223-225, May 1978

130. Crosby WM, Hill EC: Embryology of the müllerian duct system. Obstet Gynecol 20:507-515, Oct 1962

131. Fosberg JG: Derivation and Differentiation of the Vaginal Epithelium. Lund, Hakan Ohlssons Boktrycker, 1963, pp 15-61

132. Forsberg JG: Origin of vaginal epithelium. Obstet Gynecol 25:787-791, Jun 1965

133. Forsberg JG: Cervicovaginal epithelium: Its origin and development. Am J Obstet Gynecol 115:1025-1043, Apr 1973

134. Forsberg JG: Effect of sex hormones on the development of the rat vagina. Acta Endocrinol 33:520-531, Apr 1960

135. Forsberg JG: Estrogen, vaginal cancer and vaginal development. Am J Obstet Gynecol 113:83-91, May 1972

136. Cuhna GR: Stromal induction and specification of morphogenesis and cytodifferentiation of the epithelia of the müllerian ducts and urogenital sinus during development of the uterus and vagina in mice. J Exp Zool 196:361-370, 1976

137. Welch WR, Townsend DE, Robby SJ, et al: A correlation of histologic and colposcopic findings in DES-exposed females. Presented at the Society for Gynecologic Oncologists meetings, Key Biscayne, Florida, 1977

138. Townsend DE: Techniques of examination and screening of the DES-exposed female, *In* Herbst AL (Ed): Proceedings of the "Symposium on DES." The American College of Obstetricians and Gynecologists, 1978, pp 23-29

139. Taft PD, Robboy SJ, Herbst AL, et al: Cytology of clear-cell adenocarcinoma of the genital tract in young females: Review of 95 cases from the Registry. Acta Cytol 18:279-290, Jul-Aug 1974

140. Ng ABP, Reagen JW, Hawliczek S, et al: Cellular detection of vaginal adenosis. Obstet Gynecol 46:323-328, Sep 1975

141. Bibbo M, Ali I, Al-Naqeeb M, et al: Cytologic findings in female and male offspring of DES-treated mothers. Acta Cytologica 19:568-576, Nov-Dec 1975

142. Wharton JT, Rugledge FN, Gallagher HS, et al: Treatment of clear-cell adenocarcinoma in young females. Obstet Gynecol 45:365-368, Apr 1975

Refer to: Katzung BG, Gonzalez R, Scheinman MM, et al: Treatment of cardiac arrhythmias—Medical Staff Conference, University of California, San Francisco. West J Med 131: 533-543, Dec 1979

Treatment of Cardiac Arrhythmias

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, CA 94143.

DR. SMITH:* *In this conference five participants will discuss new and innovative approaches to the management of cardiac arrhythmias. The presentation will be started by Dr. Katzung.*

Basic Mechanisms of Cardiac Arrhythmias

DR. KATZUNG:† Our understanding of the basic cellular electrophysiology of cardiac arrhythmias is based largely on information provided by studies using microelectrodes.[1,2] This technique permits the recording of the transmembrane potential of individual cardiac cells and therefore, by extrapolation, indicates the relationship of cellular activity to the surface electrocardiogram.

An important result of the earliest applications of this technique[1] was the discovery that the various types of cells in the heart normally manifest rather different transmembrane action potential characteristics. In fact, each of the major tissue types within the heart—sinus node, atrial muscle, atrioventricular node, Purkinje fibers, and ventricular muscle—has its own characteristic pattern (Figure 1). The normal cardiac rhythm is the result of the integration of normal *automaticity* of the pacemaker cells of the heart—in the sinus node—with normal *conduction* of the impulse by the other cardiac cells. Therefore, normal sinus rhythm implies normal automaticity and conduction; conversely, any arrhythmia involves some abnormality of automaticity, of conduction, or of both.

A typical normal transmembrane action potential is shown schematically in Figure 2A. Fully polarized cells have a rapid upstroke (phase 0) and conduct impulses at high velocity (0.5 to 3 m per second); that is, they have "fast responses." When cardiac cells are depolarized to levels that inactivate the sodium mechanism—positive to −60 mV—they may manifest "slow-response" potentials (Figure 2B). These slow responses have been well documented in a variety of cardiac cell types[2-4] and may, in fact, represent the normal mode of activity in sinus and atrioventricular nodal cells.

Between the two extremes of normal, fast responses and slow responses, it is possible to show "depressed fast responses"; that is, action potentials that are primarily dependent on sodium channels but are sufficiently depolarized to substantially

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inactivate them.[5] The resulting conduction velocity is between 0.05 and 0.2 m per second. The characteristics of these three classes of action potential responses are summarized in Table 1.

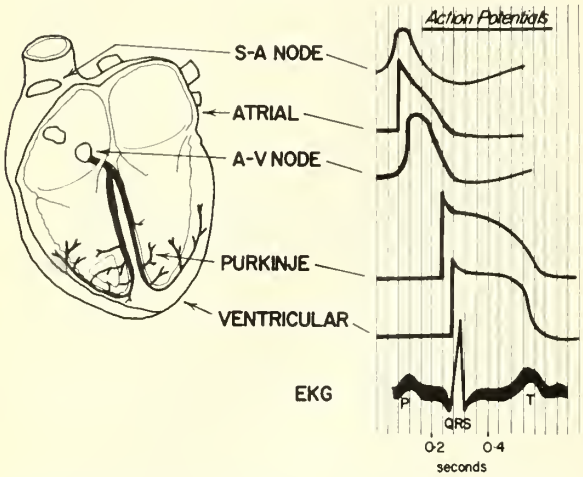

Figure 1.—Schematic diagram of various electrically important components of the heart and their typical transmembrane action potentials. Cell types that normally function as pacemakers, especially sinoatrial nodal cells, are distinguished by their diastolic depolarization and a very slow action potential upstroke. Cells in which rapid conduction is important, such as Purkinje fibers, are notable for their extremely sharp rapid upstrokes. The algebraic sum of these potentials in the extracellular space, vectored out to the body surface, yields the familiar electrocardiographic (EKG) pattern shown in the bottom tracing.

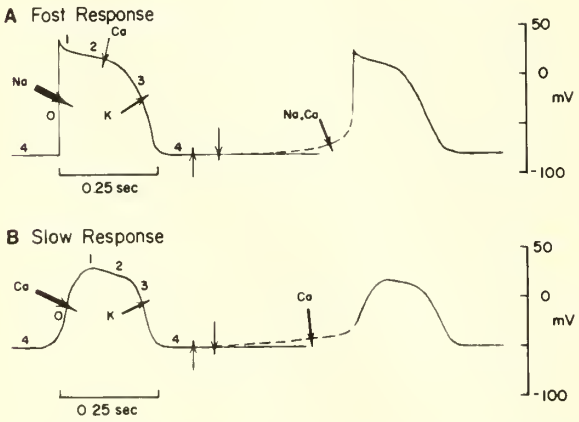

Figure 2.—**A,** Normal action potential as recorded from a ventricular fiber. During phase 0, a massive influx of sodium (Na) ions causes rapid depolarization from the resting potential of −80 to −90 mV to the overshoot level of +25 to +30 mV. A long plateau follows (phases 1 and 2) during which the membrane is kept depolarized by a small influx of calcium (Ca) ions. Repolarization (phase 3) is finally brought about by the increase of an outward potassium (K) current. During the ensuing phase 4 (electrical diastole), membrane potential remains constant if inward and outward cation fluxes (primarily sodium and potassium) are equal. However, if the inward depolarizing current exceeds the outward one, gradual diastolic depolarization (dashed line) takes place that may eventually reach the threshold (second action potential in upper tracing). Such diastolic depolarization is characteristic of automatic, or pacemaker, cells. **B,** "Slow-response" action potentials in a depolarized Purkinje or ventricular fiber. Because depolarization inactivates the sodium channels upon which the fast normal action potential depends, these depolarized cells are dependent upon the much smaller slower depolarizing effects of calcium influx. Pacemaker activity can also occur in slow-response cells.

Application of these observations to the analysis of abnormal automaticity as a cause of ventricular arrhythmias shows that several types of abnormal automaticity can be defined. Automaticity induced by depolarization, such as by *currents of injury,* has been noted by a number of investigators in many types of cardiac tissue[6] including those normally thought of as "quiescent" (for example, ventricular cells). Such automaticity usually occurs at membrane potentials characteristic of slow responses. Automaticity that occurs as a result of *metabolic* abnormalities may represent a special form of depolarization—induced automaticity. This form has clearly been shown to occur in canine Purkinje fibers exposed to high levels of carbon dioxide such as might occur after a coronary occlusion.[2]

Triggered automaticity has been documented recently in a number of cardiac preparations *in vitro.*[7] It manifests typical phase 4 depolarization like other pacemaker activity but has the unusual property of being elicited by one or several properly timed extrasystoles. It can be aborted in a similar fashion. As a result, such automaticity in the *in situ* heart could masquerade as a reentry arrhythmia because starting and stopping a tachycardia by means of properly timed stimuli have been the major criteria for the clinical diagnosis of reentry mechanism arrhythmias. A related phenomenon is that of *transient depolarizations* that appear after application of positive inotropic agents such as digitalis or epinephrine. These small depolarizations (5 to 10 mV) follow repolarization of the earlier action potential and are facilitated by increasing the preceding drive rate and extracellular calcium. With sufficient facilitation, they may reach the threshold, setting off a burst of rapid repetitive action potentials that closely resemble those of triggered automaticity.[5]

The action of antiarrhythmic drugs on automaticity appears to result from suppression of inward currents during phase 4 and a reduction in diastolic depolarization (Figure 2). The more traditional drugs like quinidine and lidocaine suppress primarily the automaticity that involves sodium influx during diastole and that arise from more negative resting potentials. Drugs like verapamil suppress automaticity in slow-response cells by blocking calcium channels.[3]

A convincing mass of evidence indicates that ventricular arrhythmias occurring in the immediate postinfarction period are usually due to re-

entry mechanisms.[8] Abnormal (slowed) conduction is of particular importance in reentry arrhythmias because conduction is involved in both of the prime requirements for reentry: unidirectional block and a conduction time greater than the effective refractory period of the cells in the circuit. These requirements are met in a variety of clinical conditions,[5,8] especially those involving anatomic abnormalities of the conducting system or ischemic heart disease. Reentry does not require anatomic obstacles, special initiating stimuli, such as extrasystoles, or very long path lengths.

Actions of Antiarrhythmic Drugs

The action of antiarrhythmic drugs on reentry mechanisms is summarized in Table 2. Most of the traditional drugs and many of the experimental ones act on sodium channels as local anesthetics; that is, they decrease conduction velocity. Thus, both quinidine and lidocaine (for instance) have the same general depressant action on the cardiac membrane. However, during each cardiac cycle, sodium channels pass through three different states—rested, activated and inactivated—before returning to the rested state. The very real distinctions between quinidine and lidocaine (and others in this class) derive from important differences in the affinities of each agent for these various channel states.[9]

Verapamil is not very potent in blocking sodium channels but substantially affects calcium channels. The resulting reduction in calcium influx is responsible for the suppressive effects of this interesting new drug[3] on slow responses. Propranolol may also exert a part of its antiarrhythmic effects via a decrease in calcium-dependent slow-response activity. This concept is based on the fact that calcium channels are very sensitive to beta adrenergic stimuli and supported by the observation that important antiarrhythmic effects can be noted for propranolol at concentrations with beta-blocking effects that are too low to have local anesthetic effects.

Finally, reentry suppression via an action on potassium channels must be considered. Amiodarone, an experimental agent, substantially prolongs cardiac action potentials and effective refractory period with little effect on conduction velocity,[3] an action best explained by potassium channel blockade. Quinidine, which also prolongs action potential duration and QT interval,[10] may exert a part of its antiarrhythmic action through this mechanism.

Mechanisms of Supraventricular Arrhythmias in Humans

Atrioventricular Node Reentry

DR. GONZALEZ:* Although evidence has accumulated to suggest that various supraventricular arrhythmias may be related to altered automaticity[11] or triggered activity,[12] the most common mechanism in patients with recurrent supraventricular tachyarrhythmias appears to be reentry.[13] Furthermore, reentry may involve "normal" cardiac conduction fibers as well as accessory pathways. The most common cause of recurrent paroxysmal tachycardia (PAT), for example, appears to be atrioventricular node reentry.[14] A proposed electric model of the atrioventricular node contains

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TABLE 1.—*Types of Cardiac Action Potentials*

Type of Potential	*Resting Potential (mV)*	*Conduction Velocity (m/sec)*	*Major Ion*	*Blocked By*
Normal fast	−100 to −75	0.2 to 3	Sodium	Quinidine (lidocaine)
Depressed fast	−76 to −60	0.05 to 0.2	Sodium	Lidocaine (quinidine)
Slow	−65 to −40	0.01 to 0.05	Calcium	Verapamil

TABLE 2.—*Action of Antiarrhythmic Drugs on Reentry Mechanisms*

Action	*Site*	*Result*	*Examples of Antiarrhythmic Drugs*
Decrease conduction velocity ..	Sodium channels	Convert unidirectional to bidirectional conduction block	Quinidine, procainamide, lidocaine, phenytoin, disopyramide, aprindine, tocainide, mexiletine
Decrease conduction velocity ..	Calcium channels	Convert unidirectional to bidirectional block	Verapamil, propranolol
Increase refractory period	Potassium channels	Refractory period becomes longer than conduction time	Amiodarone, quinidine

two longitudinally dissociated pathways (alpha and beta) in the upper portion that funnel impulses into a final common pathway[15] (Figure 3). If these pathways have differing conduction velocities and refractory periods, the proper milieu for reentry is present. A premature impulse may, for example, be blocked in one pathway but conduct via the unblocked pathway. If conduction of this premature impulse through the node is sufficiently slow, the emerging wave front may traverse the previously blocked pathway and return to the chamber of origin. Figure 3 depicts these events for a premature atrial depolarization. A reentrant arrhythmia will be sustained providing conduction velocity in this circuit is sufficiently slow so that the emerging wave front always meets excitable tissue.

Recently, techniques have become available to detect the site and mechanism of these reentrant arrhythmias more accurately. The techniques involve insertion of multipolar electrode catheters to record atrial and His bundle deflections and cardiac pacing. In addition, the cardiac cycle may be scanned with progressively premature depolarizations to initiate and terminate tachycardias. These techniques are illustrated in Figure 4. A

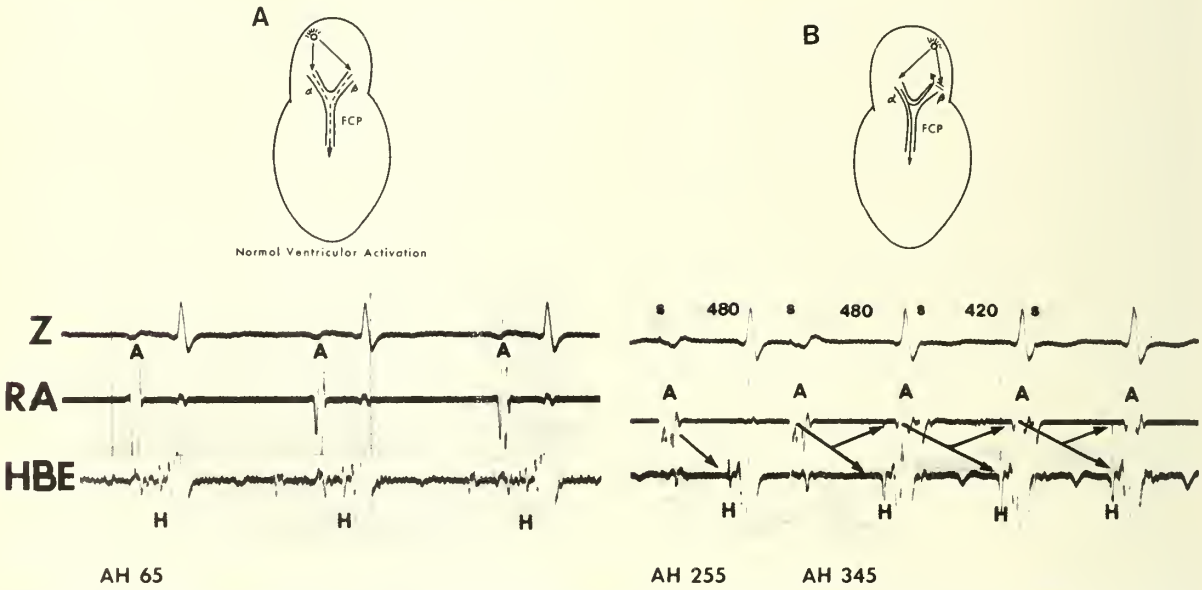

Figure 3.—Simultaneous recordings of the Z lead of the Frank orthogonal lead system and right atrial (RA) and His bundle electrograms (HBE) during sinus rhythm (A) and during induced atrioventricular nodal reentry (B). Depicted in the upper panels are electrical models of the atrioventricular node. Alpha and beta denote longitudinally dissociated pathways in the upper portion of the node that funnel impulses into a final common pathway (FCP). During sinus rhythm, the atrioventricular nodal conduction time is 65 msec. The right lower panel shows the atrium drive at a cycle length of 480 msec (S-S = 480) that results in atrioventricular nodal Wenckebach conduction. The second artial complex results in a reentrant supraventricular tachycardia whose circuit is defined by the arrows. During tachycardia, the atrial deflection coincides with QRS, thereby excluding participation of an accessory pathway. The last two stimuli occur while the atrium is still refractory.

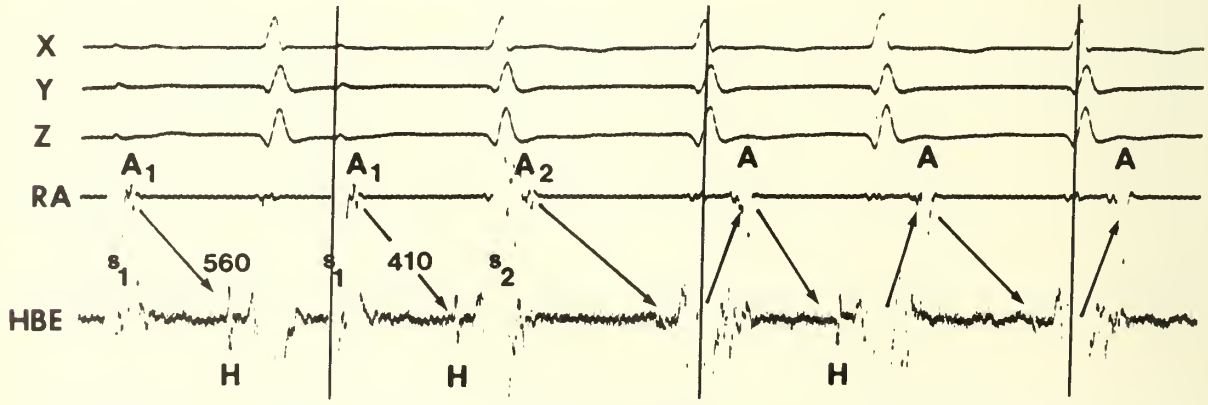

Figure 4.—Simultaneous recording of X, Y and Z leads of the Frank orthogonal lead system, right atrial (RA) and His bundle electrograms (HBE). The atrium is being paced at a cycle length of 560 msec (S_1S_1). An atrial premature beat induced at 410 msec (S_2) following the last driven atrial complex results in prolongation of the PR interval (presumably AH) and initiates a bout of supraventricular tachycardia.

critically timed premature atrial depolarization results in a crucial delay of atrioventricular nodal conduction to allow for initiation of a sustained tachycardia.

Sinoatrial or Atrial Reentry

Reentrant supraventricular arrhythmias may also occur within the atrium or involve the sinus node.[16] The basic mechanism is similar to that just described in that a premature impulse may be blocked in a portion of atrial muscle or at one margin of the sinus node and allow for initiation of a reentrant arrhythmia. Reentrant atrial or sinoatrial tachyarrhythmias commonly occur in patients with sinus node dysfunction (bradycardia-tachycardia syndrome).

Supraventricular Arrhythmias in Patients With Accessory Pathways

DR. SCHEINMAN:* Reentrant supraventricular arrhythmias may also involve an accessory pathway linking the atrium and ventricle. These pathways are known as Kent bundles and are usually involved in the tachycardia circuit. Tachycardia may develop because of differences in refractoriness between the normal (atrioventricular node-His axis) and the accessory pathway. The usual sequence of events is for a premature depolarization to block in one pathway, usually the accessory pathway, but conduct via the normal pathway and return to the chamber of origin by exciting the previously blocked pathway.[17] Possible mechanisms of supraventricular tachycardia are shown in Figure 5. Patients with the Wolff-Parkinson-White syndrome are at risk of developing two types of supraventricular arrhythmias: reentrant supraventricular tachycardia as described earlier, which is the most common type, and atrial fibrillation with rapid conduction from the atrium or ventricle via the accessory pathway. If the refractory period of the accessory pathway is sufficiently short, life-threatening ventricular arrhythmias may develop in the course of atrial fibrillation. An illustration of rapid ventricular response in a patient with Wolff-Parkinson-White syndrome and atrial fibrillation is shown in Figure 6.

Treatment of Supraventricular Arrhythmias

Supraventricular arrhythmias resulting from sinoatrial or intra-atrial reentry are best managed with classic type I antiarrhythmic drugs (quinidine, procainamide, or disopyramide). In addition, digitalis (or propranolol) may be required to impede conduction through the atrioventricular node. It should be emphasized that these arrhythmias may occur in patients with sinus node dysfunction, and the antiarrhythmic drugs alluded to may further suppress sinus activity. In the latter situation, consideration must be given to insertion of a permanent cardiac pacemaker to enable optimal use of the required drugs.

In patients with intranodal reentry, initial emergency treatment involves use of vagotonic maneuvers or drugs.[18] Vagal maneuvers (carotid

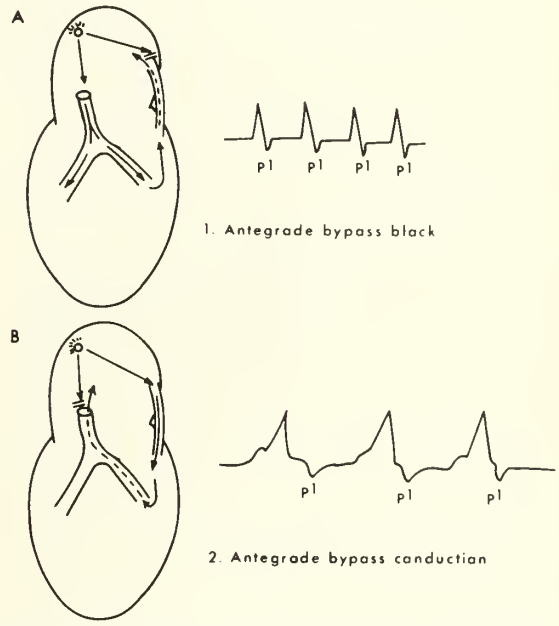

Figure 5.—In patients with the Wolff-Parkinson-White syndrome and paroxysmal supraventricular tachycardia, the reentrant circuit is usually maintained by antegrade conduction down the atrioventricular node-His bundle axis and retroconduction via the Kent bundle. **A,** The electrocardiogram will show normal QRS. **B,** Rarely there will be antegrade conduction via the accessory pathway and retroconduction via the atrioventricular node-His axis. (Reprinted with permission from Scheinman.[18])

Figure 6.—Atrial fibrillation with ventricular preexcitation in a patient with the Wolff-Parkinson-White syndrome. The shortest preexcited RR interval during atrial fibrillation was 240 msec. (Abbreviations as in Figure 3.)

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sinus pressure, Valsalva's maneuver) act to impede conduction and prolong refractoriness in the atrioventricular node, and may, therefore, extingush intranodal reentrant arrhythmia. Similarly, digitalis, propranolol, or both, have similar effects on the atrioventricular node and have also been found to be effective in arrhythmia termination. Verapamil is an experimental drug that acts to block transmembrane calcium flux and, hence, has predominant effects on the slow-response cells. In clinical usage this drug has variable effects on sinus rate but induces substantial increases in atrioventricular nodal conduction time; it is presently the drug of choice in Europe for treatment of paroxysmal supraventricular tachycardia. The classic type I drugs appear to be less useful for acute arrhythmia control but may be effective for chronic prophylaxis. These agents may be effective either because of suppression of the premature beat that initiates the tachycardia or because of their influence on prolonging intraatrial refractoriness so that return impulses from the atrioventricular node find an inexcitable atrium.

Drug Therapy for Arrhythmias in Patients With the Wolff-Parkinson-White Syndrome

The acute management of patients with the Wolff-Parkinson-White syndrome and paroxysmal supraventricular tachycardia is similar to that for patients with intranodal reentry. One important exception is avoidance of digitalis because this drug may shorten the refractory period of the accessory pathway.[19] If atrial fibrillation should develop subsequently, ventricular fibrillation may also occur because of an extremely rapid ventricular response.[20] Patients with the Wolff-Parkinson-White syndrome who present with atrial fibrillation and extremely rapid ventricular response should be treated with emergency direct current cardioversion. After reversion to sinus rhythm, the patient should receive intravenous procainamide because this drug may be administered safely intravenously and it usually results in prompt prolongation of the refractory period of the accessory pathway. Chronic oral therapy with one of the type I drugs should be initiated, but the patient should undergo electrophysiologic studies including induction of atrial fibrillation, to be certain that the drug is, in fact, effective in controlling the ventricular response during atrial fibrillation (Figure 7). If a drug or drug combination cannot be found to control the ventricular response to atrial fibrillation adequately, surgical extirpation of the accessory pathway is indicated (see subsequent section).

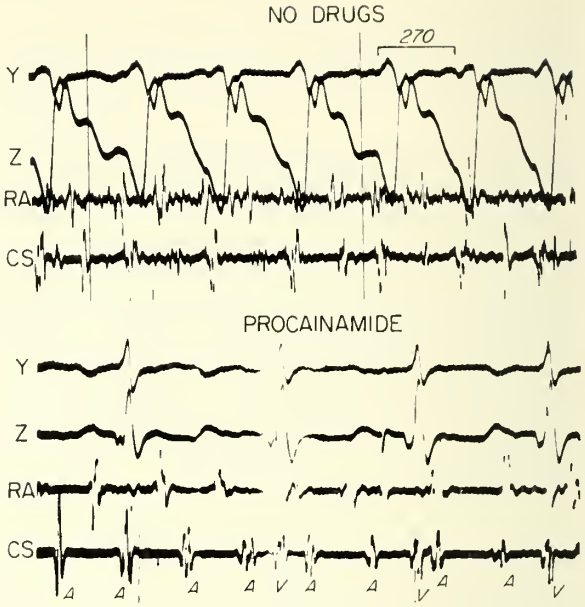

Figure 7.—The upper panel shows atrial fibrillation with rapid ventricular response; all QRS deflections show maximal preexcitation. Thus, there is a rapid rate due to antegrade conduction down the accessory pathway. In the lower panel, atrial flutter induced after intravenous infusion of procainamide shows 2:1 atrioventricular block. The QRS complexes are now conducted down the normal atrioventricular node-His axis (narrow QRS complexes) and there is complete block in the accessory pathway. (RA = right atrium; CS = coronary sinus.)

Management of Patients With Supraventricular Arrhythmias Refractory to Drug Therapy

If a patient has recurrent bouts of paroxysmal supraventricular tachycardia or atrial fibrillation and flutter that are unresponsive to medical management, electrophysiologic studies are indicated to define the mechanisms and tachycardia circuit, to assess the possible benefits of radiofrequency pacemaker insertion, or to determine the type of surgical approach required. In patients with paroxysmal supraventricular tachycardia, atrial overdrive pacing may be effective in terminating the tachycardia by either overdrive suppression of a focal tachycardia or, more likely, by rendering the atrium refractory to return impulses (from either the atrioventricular node or an accessory pathway). This method involves insertion of electrodes into the atrium either via a vein or by direct implantation at the time of thoracotomy. The electrodes are connected to a subcutaneously implanted radiofrequency receiver with the patient carrying a transmitter. When the tachycardia is

perceived, the transmitter is activated by the patient and electric impulses are delivered to the atrium at rates determined during electrophysiologic evaluation (Figure 8). Our experience with this technique has been detailed previously.[21] In brief, of eight patients treated with radiofrequency pacing, one with the Wolff-Parkinson-White syndrome subsequently required a surgical operation because of recurrent atrial flutter with rapid ventricular response; the remainder are well controlled by either the pacemaker alone or with concurrent drug therapy to decrease the number of episodes of tachycardia.

Surgical Procedures for Patients With Supraventricular Tachycardia

DR. THOMAS:* Patients who are refractory to drug or pacemaker therapy should be considered for cardiac electrosurgical procedures. Such operations should never be undertaken without previous careful electrophysiologic studies to define precisely the tachycardia circuit. In our experience over the past three years, eight patients with recurrent supraventricular tachycardia without evidence of an accessory atrioventricular nodal pathway underwent His bundle section and insertion of a permanent ventricular pacemaker. The His bundle was located by means of a hand-held bipolar electrode probe, which was used to explore the area between the coronary sinus and septal leaflet of the tricuspid valve (Figure 9). The incision was made through the area showing the maximal His bundle deflection. One patient died three days after the surgical procedure following a massive cerebrovascular event, and in one patient atrioventricular conduction returned approximately six weeks after the operation. In this latter patient, supraventricular tachycardia is currently well controlled with drug therapy. The remaining six patients are asymptomatic, have returned to normal activities, and are taking no cardiac medications.

Five patients with the Wolff-Parkinson-White syndrome underwent cardiac electrosurgery in an effort to control drug-resistant recurrent supraventricular arrhythmias. One patient had a right anterior accessory pathway, one had a posterior septal pathway and three had left free-wall pathways. One of these patients with severe cardiomyopathy and mitral regurgitation died three weeks after the surgical procedure, three patients are asymptomatic without drug therapy, and one patient had a return of accessory pathway conduction although arrhythmias are currently responsive to drug therapy.

*Arthur N. Thomas, MD, Associate Professor, Department of Surgery, and Chief, Thoracic Surgery, San Francisco General Hospital Medical Center.

Ventricular Tachycardia

There appears to be an increased incidence of cases of recurrent ventricular tachycardia. This arrhythmia occurs often in patients with ischemic heart disease. The standard therapeutic approach involves empiric use of available antiarrhythmic drugs with continuous monitoring of the patient's rhythm during both normal activity and exercise stress testing.[22] Two major limitations of this technique are the length of time required to obtain an optimal treatment regimen and the fact that some patients have few or no premature ventricular depolarizations during tachycardia-free periods.

An important innovation in the management

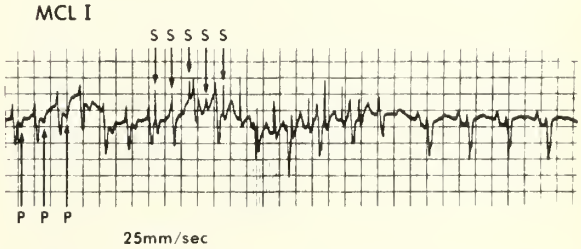

Figure 8.—Surface lead MCL I shows supraventricular tachycardia at a rate of 250 beats per minute. The inverted P waves are labeled during the tachycardia. Activation of the radiofrequency pacemaker(s) results in atrial capture at a rate of 290 beats per minute and tachycardia termination. (Reprinted with permission from Peters et al.[21])

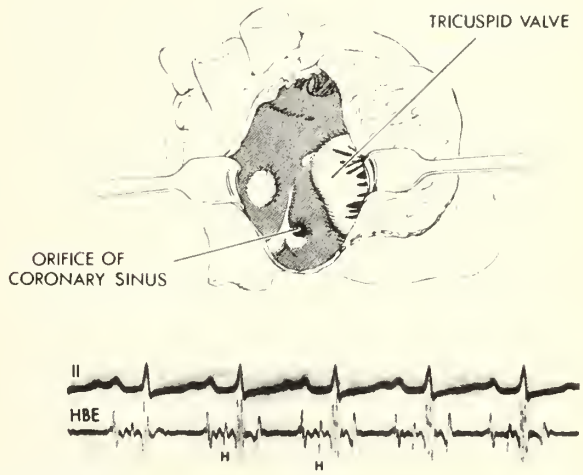

Figure 9.—The upper panel details the surgical landmarks used in identification of the His bundle. A hand-held bipolar electrode probe is used to explore the area between the orifice of the coronary sinus and the septal leaflet of the tricuspid valve. An illustration of a His bundle deflection (H) obtained during endocardial mapping is shown in the bottom panel.

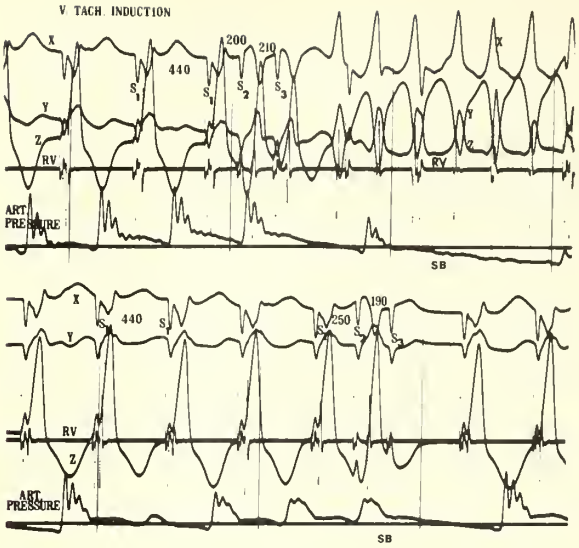

Figure 10.—Top, Simultaneous recordings of X, Y and Z leads of the Frank orthogonal lead system together with the right ventricular (RV) electrogram and arterial (ART) pressure curve. Sustained ventricular tachycardia was induced by insertion of two ventricular extrastimuli (S_2S_3) 200 and 210 msec, respectively, after the last driven complex (S_1). **Bottom,** After administration of procainamide, the ventricular effective refractory period lengthened and double extrastimuli (S_2S_3) failed to provoke ventricular tachycardia.

of these patients includes insertion of an electrode catheter into the apex of the right ventricle for purposes of ventricular stimulation. The study protocol calls for both short periods of rapid ventricular overdrive and insertion of one or more programmed ventricular extrastimuli throughout the ventricular diastolic cycle in an effort to provoke ventricular tachycardia.[23] The patient then undergoes serial electropharmacologic testing to determine which drug(s) prevents induction of tachycardia (Figure 10). These studies should, of course, be undertaken only in proper facilities under careful supervision. The short-term experience of using this technique in patients with recurrent ventricular tachycardia appears to be especially promising. In a collective review[24] of 90 patients who underwent serial drug testing during ventricular stimulation, 56 followed a drug regimen that had been predicted in the laboratory to provide complete control of their tachycardia and only 5 percent of these patients had recurrence of ventricular tachycardia or died suddenly. In contrast, 15 of 20 patients (75 percent) in whom an adequate drug regimen could not be found subsequently developed a recurrence of ventricular tachycardia or died suddenly. The benefits of the ventricular stimulation approach allow for relatively rapid detection of a drug regimen predictive of successful arrhythmia control. The risks include induction of ventricular tachycardia or ventricular fibrillation; therefore, the procedure must be done by personnel expert in cardiopulmonary resuscitation.

Surgical Management of Ventricular Tachycardia in Patients With Coronary Artery Disease

Dr. Ullyot:* The standard approach to the management of patients with recurrent ventricular tachycardia and coronary artery disease includes coronary revascularization, aneurysmectomy or both. Although the current literature contains many reports[25-30] dealing with the standard surgical approach, many questions remain unanswered. Most studies tend to emphasize successful results. Most are either case reports or summaries of small series that fail to delineate carefully the preoperative medical regimen with respect to drugs used, measurement of blood levels of each drug and patient compliance. Moreover, results are reported in terms of survival statistics while the findings of continuous electrocardiographic monitoring relative to subsequent incidence of tachyarrhythmias are not given. Nonetheless, the data show an overall operative mortality of 18 percent with good results in terms of arrhythmia management in many patients.

A recent study by Mason and colleagues[31] is perhaps the best source of information relative to this question. They report the results of 57 surgical procedures carried out over seven years for the primary indication of ventricular tachyarrhythmia in 56 patients with ischemic heart disease. Preoperative evaluation included hemodynamic studies, coronary arteriography, and left ventriculography with documentation of the recurrent nature of the arrhythmias and refractoriness to drug management. A majority of patients (58 percent) underwent combined left ventricular aneurysmectomy and coronary artery bypass grafting. Another 28 percent of the patients had aneurysmectomy alone and 14 percent had coronary artery bypass grafting alone. There were 11 intrahospital deaths or a 20 percent operative mortality, and seven of the 11 deaths were due to arrhythmias. In addition, 10 deaths occurred late in the follow-up period or at an average of 22 months. Only one of the late deaths was sudden and, therefore, presumably due to an arrhythmia. Of the 35 survivors, only 11 percent (4

*Daniel J. Ullyot, MD, Associate Professor, Department of Surgery.

of 35) had symptomatic tachyarrhythmia. Antiarrhythmic drug therapy was required in 57 percent (20 of 35 patients). Fifteen patients had ambulatory Holter monitoring studies and four showed bouts of ventricular tachycardia. This important study shows that standard surgical techniques can be applied successfully to patients with ischemic heart disease and refractory ventricular arrhythmia with good results in many patients and with an operative mortality of approximately 20 percent. Most deaths occurred in patients with recent acute myocardial infarction or poor left ventricular function.

In an attempt to improve the standard approaches, three additional surgical procedures have evolved. The first is determining the location of the tachycardia focus by epicardial mapping following the induction of ventricular tachycardia during the operation and then carrying out a ventriculotomy over the area of earliest activation. However, this approach met with limited success.

The same group then developed a second technique; namely, "encircling myotomy."[32] The technique consists of opening the left ventricle through a scarred segment and making a nearly full-thickness incision in the left ventricular endocardium at the edge of the visible endocardial scar. The incision is made perpendicular to the plane of the endocardium and is carried circumferentially around the junction of the aneurysm and normal left ventricular muscle at the edge of the endocardial scar. The incision is extended near to but not through the epicardium and care is taken not to injure the coronary arteries. The incision is closed using a continuous suture from within the left ventricular cavity.

The rationale for this procedure is to create a barrier between the aneurysm or scar and the normal muscle, and stems from recent epicardial mapping studies which showed that the origin of the tachycardia is almost always located at the border of the aneurysm. The encircling myotomy, then, provides an effective barrier that prevents reentrant ventricular arrhythmia. It should be emphasized that this border zone is usually not excised with conventional aneurysmectomy as the standard technique leaves a rim of scar tissue to ensure a secure closure. The arrhythmic focus is often located in the ventricular muscle within 2 cm of the aneurysmal scar. This may explain why the conventional approach often fails to result in tachycardia control. The originators of this technique reported on five cases of drug-resistant ventricular tachycardia that were treated with encircling myotomy.[32] There were no operative deaths among the patients and drug therapy was discontinued postoperatively. No ventricular tachycardias recurred during a follow-up period of 6 to 24 months; these studies included ambulatory Holter monitoring.

The third surgical approach to treatment of recurrent ventricular tachycardia with coronary artery disease is that of endocardial excision.[33] This technique involves the use of intraoperative epicardial and endocardial mapping during induced ventricular tachycardia, paying particular attention to mapping the edges of the aneurysm. Conventional aneurysmectomy is then done and programmed ventricular tachycardia repeated. On the basis of the data obtained during tachycardia, endocardial excision is carried out in the area determined to be the origin of the arrhythmia. Those patients with substantial coronary obstructive lesions and distal vessels suitable for bypass then undergo coronary artery bypass operation. The investigators reported on 12 patients treated with this technique; there was one operative death. Postoperatively, all patients had repeated electrophysiologic studies after antiarrhythmic agents had been discontinued and in none could ventricular tachycardia be initiated. Two interesting additional observations were made in the study. In 11 of the 12 patients, tachycardia could still be induced intraoperatively after standard aneurysmectomy. This observation tends to support the notion that conventional aneurysmectomy may not be effective for arrhythmia control. One patient did not have an aneurysm, and the arrhythmic focus was detected in the posterior third of the intraventricular septum, which was excised through a ventriculotomy into normal muscle.

We have developed a surgical approach that is somewhat different from the other methods. Patients with recurrent ventricular tachycardia refractory to drug management are studied preoperatively with programmed ventricular stimulation, and after ventricular tachycardia is induced, endocardial mapping is carried out to locate the earliest areas of depolarization during tachycardia.[33] Coronary arteriography and left ventriculography are then done before electrophysiologic studies are carried out.

Coronary artery bypass grafting is done initially using moderate hypothermia (32°C) with intermittent aortic occlusion during construction of

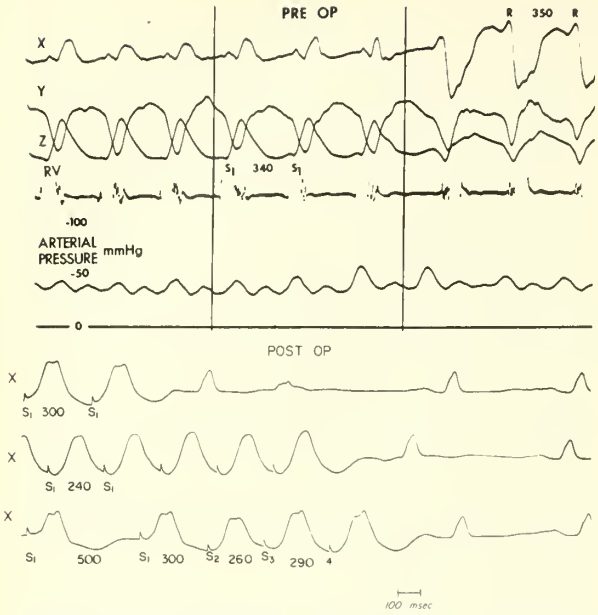

Figure 11.—Top, Preoperative (PRE OP) findings in a patient with recurrent ventricular tachycardia (VT) (abbreviations as in Figure 10). VT is induced after ventricular pacing at a cycle length of 340 msec. The tachycardia cycle length = 350 msec. **Bottom,** Postoperatively (POST OP), ventricular tachycardia could not be induced either with rapid ventricular overdrive pacing (CL=300, 240 msec) or by insertion of multiple ventricular extrastimuli.

a distal anastomosis. The reason for doing a coronary artery bypass first is based on two considerations. (1) Our studies of myocardium metabolism using coronary sinus catheterization showed that ischemia commonly occurs during standard coronary artery bypass operation and we believe that subsequent intraoperative electrophysiologic studies are safer when revascularization is carried out first. (2) We speculate that the augmented myocardial blood flow may change electrophysiologic events; therefore, we prefer to study patients in a state more nearly approximating their postoperative condition. In this way, we are able to assess tachycardia inducibility after coronary revascularization. In patients with either an aneurysm or large areas of scar tissue, we then excise scar tissue in the usual manner. At this point, reference and pacing electrodes are inserted on the right and left ventricular myocardia, respectively, while the patient is warmed to 38°C. Ventricular tachycardia is induced during total cardiopulmonary bypass by programmed ventricular stimulation, and epicardial and endocardial mapping is carried out, with particular attention given to the borders of the myocardial resection and to areas of interest located preoperatively. Resection of the arrhythmogenic focus is then done, the ventricle closed, air evacuated from the heart and cardiopulmonary bypass discontinued.

During the past six months, we have used this technique in treating seven patients. All patients underwent coronary artery saphenous vein bypass grafts. Five of the seven had concomitant aneurysmectomy or excision of scar tissue in addition to subendocardial resection. In two patients, no resection was carried out because the tachycardia could not be induced after revascularization. One death occurred suddenly and late (presumably from an arrhythmia); ventricular tachycardia could not be stimulated in this patient intraoperatively.

Our research protocol has involved restudy of all patients six to eight weeks after their surgical operation. These studies include continuous electrocardiographic monitoring for at least 24 hours, exercise stress testing and repeat ventricular stimulation studies (Figure 11). To date, three patients are asymptomatic without antiarrhythmic drug therapy, three are asymptomatic while receiving standard antiarrhythmic drug therapy, and two of the three have not undergone repeat testing so that long-term need for therapy is not known. Although the reported series is small, we believe that techniques of cardiac mapping and resection of arrhythmogenic foci coupled with bypass grafting may offer improved results over coronary artery bypass operation and standard aneurysmectomy alone.

In summary, recent advances in our understanding of basic mechanisms of tachyarrhythmias have enabled development of newer approaches in the management of patients with tachyarrhythmias. In most patients, tachycardia can be controlled by appropriate drug therapy; promising experimental drugs such as the calcium blockers appear to effect excellent results in patients with supraventricular tachycardia. In patients who prove to be resistant to drug therapy, consideration should be given to the use of cardiac pacing or cardiac electrosurgical procedures in which His bundle or accessory pathway ablation or excision of ventricular arrhythmogenic foci may be carried out as described.

REFERENCES

1. Coraboeuf D: Ionic basis of electrical activity in cardiac tissues. Am J Physiol 234:H101-H116, Feb 1978

2. Coraboeuf E, Deroubaix E, Hoerter J: Control of ionic permeabilities in normal and ischemic heart. Circ Res 38 (Suppl I): 192-197, May 1976

3. Zipes DP, Besch HR, Watanabe AM: Role of the slow current in cardiac electrophysiology. Circulation 51:761-766, May 1975

4. Spear JF, Horowitz LN, Hodess AB, et al: Cellular electrophysiology of human myocardial infarction—I. Abnormalities of cellular activation. Circulation 59:247-256, Feb 1979

5. Wit AL, Cranefield PF: Reentrant excitation as a cause of cardiac arrhythmias. Am J Physiol 235:H1-H17, Jul 1978

6. Katzung BG: Automaticity in cardiac cells. Life Sci 23: 1309-1315, Oct 1978

7. Vassalle M: Cardiac automaticity and its control. Am J Physiol 233:H625-H634, Dec 1977

8. El-Sherif N, Scherlag BJ, Lazzara R, et al: Re-entrant ventricular arrhythmias in the late myocardial infarction period—1. Conduction characteristics in the infarction zone. Circulation 55: 686-702, May 1977

9. Hondeghem LM, Katzung BG: Time- and voltage-dependent interactions of antiarrhythmic drugs with cardiac sodium channels. Biochim Biophys Acta 472:373-398, Nov 1977

10. Edwards I, Hancock BW, Sayner R: Correlation between plasma quinidine and cardiac effects. Br J Clin Pharmacol 1:455-459, 1974

11. Scheinman MM, Basu D, Hollenberg M: Electrophysiologic studies in patients with persistent atrial tachycardia. Circulation 50:266-273, Aug 1974

12. Hordof AJ, Edie R, Malm JR, et al: Electrophysiologic properties and response to pharmacologic agents of fibers from diseased human atria. Circulation 54:774-779, Nov 1976

13. Kulbertus HE (Ed): Re-entrant Arrhythmias: Mechanisms and Treatment. Baltimore, University Park Press, 1977

14. Wu D, Denes P, Amat-y-Leon F, Dhingra R, et al: Clinical electrocardiographic and electrophysiologic observations in patients with paroxysmal supraventricular tachycardia. Am J Cardiol 41:1045-1051, May 1978

15. Moe GK, Mendez C: The physiologic basis of reciprocal rhythm. Prog Cardiovasc Dis 8:461-482, Mar 1966

16. Paulay KL, Varghese PJ, Damato AN: Sinus node reentry: An in vivo demonstration in the dog. Circ Res 32:455-463, Apr 1973

17. Gallagher JJ, Gilbert M, Svenson RH, et al: Wolff-Parkinson-White syndrome—The problem, evaluation, and surgical correction. Circulation 51:767-785, May 1975

18. Scheinman MM: The treatment of paroxysmal supraventricular tachycardia. Ration Drug Ther 10:1-6, May 1976

19. Sellers TD Jr, Bashore TM, Gallagher JJ: Digitalis in the preexcitation syndrome—Analysis during atrial fibrillation. Circulation 56:260-267, Aug 1977

20. Sellers TD Jr, Campbell RWF, Bashore TM, et al: Effects of procainamide and quinidine sulfate in the Wolff-Parkinson-White syndrome. Circulation 55:15-22, Jan 1977

21. Peters RW, Shafton E, Frank S, et al: Radio-frequency-triggered pacemakers: Uses and limitations. Ann Intern Med 88: 17-22, Jan 1978

22. Lown B, Graboys TB: Management of patients with malignant ventricular arrhythmias. Am J Cardiol 39:910-918, May 1977

23. Horowitz LN, Josephson ME, Farshidi A, et al: Recurrent sustained ventricular tachycardia—3. Role of the electrophysiologic study in selection of antiarrhythmic regimens. Circulation 58: 986-997, Dec 1978

24. Fisher JD: Ventricular tachycardia—Practical and provocative electrophysiology. Circulation 58:1000-1001, Dec 1978

25. Couch OA Jr: Cardiac aneurysm with ventricular tachycardia and subsequent excision of aneurysm. Circulation 20:251-253, Aug 1959

26. Favaloro RG, Effler DB, Groves LK, et al: Ventricular aneurysm—Clinical experience. Ann Thorac Surg 6:227-245, Sep 1968

27. Kremer R, Chalant C, Ponlot R, et al: Tachycardie ventriculaire recidivante guerie par resection d'un aneurisme parietal du ventricule gauche. Acta Cardiol 24:523-530, 1969

28. Hunt D, Sloman G, Westlake G: Ventricular aneurysmectomy for recurrent tachycardia. Br Heart J 31:264-266, 1969

29. Magidson O: Resection of postmyocardial infarction ventricular aneurysms for cardiac arrhythmias. Dis Chest 56:211-218, Sep 1969

30. Ritter ER: Intractable ventricular tachycardia due to ventricular aneurysm with surgical cure. Ann Intern Med 71:1155-1157, Dec 1969

31. Mason JW, Buda AJ, Stinson EB, et al: Surgical therapy of ventricular tachyarrhythmias in ischemic heart disease using conventional techniques. Am J Cardiol (In Press)

32. Guiraudon G, Fontaine G, Frank R, et al: Encircling endocardial ventriculotomy: A new surgical treatment for life-threatening ventricular tachycardias resistant to medical treatment following myocardial infarction. Ann Thorac Surg 26:438-444, Nov 1978

33. Josephson ME, Harken AH, Horowitz LN: Endocardial excision: A new surgical technique for the treatment of recurrent ventricular tachycardia. Circulation 61:1430-1439, Dec 1979

Causes of Gastritis

GASTRITIS is a condition which until recently has not been truly appreciated in terms of its depth . . . both in the incidence and the degree of morbidity it can produce in the patient population. But, since we began using the flexible gastroscope, it is recognized much more frequently; . . . it is not an increase of incidence . . . just an increased recognition rate. Some factors that play a role in acute gastritis are stress, infection and alcohol, aspirin, phenylbutezone (Butazolidin) and other chemicals . . . and most cases of acute gastritis result from chemical irritation to the mucosa.

—GERALD KLEBANOFF, MD, *Youngstown, Ohio*
ROBERT P. HUMMEL, MD, *Cincinnati, Ohio*

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EDITORIALS

Alternative Methods of Health Care

In this issue the editors present several papers addressing the humanistic medicine and holistic health movement, its meaning and relationships to orthodox medicine. These papers are intended to begin a forum that will continue for several issues. No attempt was made to list or to describe the many and varied activities which have found or seek a place within these concepts. Rather the papers are by persons considered to be knowledgeable in some of the broader aspects of the subjects, who also have familiarity with orthodox or allopathic medicine.

It will be noted that all of these first papers originated in California. A perusal of a compendium of resources for persons interested in this growing movement[1] indicates that there has been far more interest in these "alternative" methods of health care in California than almost anywhere else, although there is good evidence that this interest has begun to spread throughout the West and elsewhere. It is hoped that as responses come in from other states, they will be as well represented as California in the forum as it develops.

It is easy to dismiss movements such as this as being mostly unscientific quackery practiced by charlatans whose primary purpose is personal gain. To some extent this may indeed be the case, but it may not be wholly so. The quackery aspects of the subject, whatever they may be, are only lightly touched upon in this series of papers. Rather the focus is more upon the meaning of what is occurring and what might be its importance for medicine, for patient care, and for improving the health and well-being of mankind in this interdependent world. No doubt much will be added and many things will be rounded out by further comments from readers and others.

—MSMW

REFERENCE

1. The Holistic Health Handbook—Compiled by the Berkeley Holistic Health Center. Berkeley, CA, And/Or Press, 1978

Treatment of Cardiac Arrhythmias

Elsewhere in this issue appears a Medical Staff Conference on the treatment of cardiac arrhythmias. The subject is both important and timely, in large measure because disturbances of cardiac rhythm constitute a major cause of morbidity and mortality from cardiovascular disease. No single area of basic or clinical cardiovascular investigation has received greater emphasis within the last five years. As a consequence of those investigations, most of us feel that we are on the threshold of a major breakthrough in treatment, to which medical and surgical approaches will contribute importantly. There are five presentations in this conference, covering physiology, pharmacology, medical evaluation, medical treatment and surgical treatment. The contributors and their subjects represent the views of the continuum of investigators in their field. The authors have presented the positive side of the information and balance. I will highlight a few of those points, but also identify certain areas in each category where there are gaps in our information and where more investigation is necessary.

Emphasis has been placed in the last ten years on the application of microelectrode studies to understanding the action potential, differences between various regions of the heart and the ionic basis for the action potential. Many data that contribute to our understanding of normal impulse formation and conduction are available. In contrast, we know very little about the effects of disease on electrical properties of the cardiac cell and on the nature of couplings between cells that determine their electrophysiologic characteristics. Certainly, one of the new frontiers in cardiac electrophysiology will be the systematic and careful analysis of the action potential and membrane properties of diseased human tissues. Without this information we are not likely to have a firm foundation on which to understand the basis of alterations of rhythm in man.

Physiologists and pharmacologists have adapted methods developed for nerve studies to the study of heart muscle. They have used these methods to gain insights regarding the changes of membrane conductance that are responsible for the action potential and alterations of membrane conductance occurring as a consequence of cardiac drugs. We are already at a stage in which antiarrhythmic drugs have been classified on the basis of their effects on the action potential and membrane conductance and we are moving in the direction of finding drugs that are more and more specific in their effects on selective membranes. The practical goal of developing new drugs is to increase the number of effective agents that are available for the treatment of alterations of rhythm in man. An intellectual application of this information is based on the concept that the effective use of drugs that have a highly specific action will ultimately help to clarify the mechanisms of arrhythmias in man.

Despite the logic of this approach there are certain shortcomings that should be recognized. First, the methods that have been used so successfully in nerve studies to define membrane conductance have serious shortcomings when applied to cardiac muscle. Consequently, we are not able to be completely confident in the conclusions that have been derived from such studies. A second important point is that most of the antiarrhythmic agents that are used effectively in man today appear to have more than one action on excitable cells. Which of these actions is the one responsible for the antiarrhythmic effect in any given situation is uncertain. Until we have an understanding of the effects of disease on human cardiac tissues, it may prove hazardous to extrapolate from studies of the effects of pharmacologic agents on normal tissues to their effects on abnormal tissues. The pharmacology of diseased tissue will be a second frontier in future electrophysiologic investigations.

The ability to record electrical signals from a cavity of the heart and from the specialized conduction system has contributed importantly to our understanding of cardiac arrhythmias in man. Using this technique we can understand sinus node and atrioventricular node function, intraatrial and interatrial conduction, and intraventricular and interventricular conduction during disturbances of cardiac rhythm. These techniques have proved especially useful in evaluating pathophysiology and the response to treatment of patients with supraventricular tachycardia, the Wolff-Parkinson-White syndrome and ventricular tachycardia. The shortcomings of these techniques are essentially the shortcomings of any modeling experiment. Catheter studies are based on recording extracellular potentials from selected sites and evaluating their response during normal rhythm and abnormal rhythms and after an electrical stimulus. The interpretation of an electrophysiologic study is based on assumptions regarding the relationship between the extracellular waveform and intracellular events and on the behavior of the system that is being studied. For example, we record the input and the output from the atrioventricular node on a typical His bundle electrogram, but the interpretation of what happens between the atrial and His bundle signals is based almost entirely on theories regarding the behavior of the atrioventricular node.

Catheter studies have contributed to our understanding of a host of disturbances of cardiac rhythm. At each step, however, the interpretation of the studies is only as good as the underlying information derived from more sophisticated studies. For example, for some time it was felt that any form of reentrant tachycardia initiated by a premature atrial beat that fell in the relative refractory period of the atrioventricular node must be attributable to atrioventricular nodal reentry. We now know that that is not the case and that accessory pathways that conduct in the retrograde direction account for a significant percentage of such events. For many years we felt that initiation of a regular tachycardia by premature stimulation defined a reentrant arrhythmia. We now know that that is not the case. There is the phenomenon of triggerable automaticity. It will be vitally important in years ahead to maintain a close relationship between basic and applied clinical electrophysiology to assure that the concepts derived from basic studies are incorporated into the models that are used for the interpretation of clinical studies.

Probably the first form of surgical treatment used to correct disturbances of cardiac arrhythmias was the successful use of thoracic sympathectomy by Smithwick and his colleagues more than 40 years ago to treat atrial and ventricular tachycardia. Surgical procedures played such a vital role in the development and application of pacemakers that pacemaker treatment should also be included in a review of surgical treatment of alteration of rhythm and conduction. The issue

that has been introduced in this month's symposium is the concept of specific ablative procedures designed to eliminate the tissues responsible for cardiac arrhythmias in man and hence to assure a normal and stable cardiac rhythm. This field of interest developed about 12 years ago with the first successful treatment of a patient with the Wolff-Parkinson-White syndrome by dividing the accessory pathway. Subsequent to that report surgical treatment of this syndrome has been developed to a high degree of sophistication. It is widely applicable and for all practical purposes uniformly successful. It brought the electrophysiologists to the operating room and resulted in the development of much more sophisticated mapping techniques. With the availability of these techniques surgical treatment of arrhythmias has been extended to other forms of atrial tachycardia, atrioventricular nodal tachycardia and ventricular tachycardia. In each of these areas enough successes have been reported to indicate the feasibility of this approach and to suggest that further development of methods for surgical treatment of many forms of cardiac arrhythmias is desirable.

Here again, certain problems can be anticipated. Not all arrhythmias inducible in the catheterization laboratory are induced with equal ease or at all under anesthesia. In my judgment the anesthesiologist will become the next important member of the team for the study of disturbances of cardiac rhythm in man. Together with surgeons, cardiologists and pharmacologists, anesthesiologists must develop techniques to assure that arrhythmias that occur in awake patients can also be precipitated in anesthetized patients for purposes of study.

A second problem involves the mapping technique itself. It is remarkable that we have gained as much insight into the electrical activation of the heart as we have with available mapping techniques. We were extremely fortunate in studying the Wolff-Parkinson-White syndrome, that mapping could be done repeatedly, with a stable rhythm and in patients who were basically healthy and tolerated the arrhythmia well. This is not the situation in ventricular tachycardia. In this situation all of the necessary information is not likely to come from epicardial maps. Transmural recordings will also be necessary. Computer techniques will be necessary to facilitate the acquisition and interpretation of data. Particularly in the area of ischemic heart disease it seems highly probable that the regions responsible for arrhythmias are deep in the epicardial structures and in some instances within the septum. These considerations make mapping and the interpretation of maps within the framework of a cardiac surgical procedure much more complex.

A third problem involves surgical risk. In patients with the Wolff-Parkinson-White syndrome, who are usually healthy except for their arrhythmia, mapping techniques are relatively simple and the surgical procedures aimed at correcting the disturbance are relatively nondestructive. As a consequence, operative risk is low and surgical success is high. As we move into the application of surgical techniques to the treatment of more complex arrhythmias, other hurdles must be overcome. These procedures are being carried out on patients who have serious forms of heart disease and alterations in cardiac performance including congestive heart failure. The surgical operation is long and complex and some of the approaches described in this conference involve rather extensive dissections of ventricular tissue with uncertain effects on global left ventricular function. How far we can go in the direction of more extensive surgical procedures on progressively sicker patients remains to be determined.

From an internist's point of view, I think we recognize that all forms of cardiac surgical treatment involve some acute impairment of cardiac function as a consequence of anesthesia, manipulation and cardiopulmonary bypass. This is balanced by the direct improvements that can be expected as a consequence of the surgical procedure. This balance of effects is true whether we are talking about valvular heart disease, congenital heart disease, coronary bypass operations or the treatment of arrhythmias.

Most patients who are potential candidates for operations to correct ventricular arrhythmias have seriously deranged ventricular function. I believe that the emphasis in the next several years will be on developing mapping techniques that shorten the time required to obtain the necessary information about the arrhythmias and that maximize the value of the data for localizing tissue that is critical to the mechanism of the arrhythmia. In parallel with this, dissection and other less invasive techniques such as cryoablation will be explored so that the ablative procedure itself is short and has minimal effects on cardiac function. These will be important steps if we are to reach the potential of applying surgical techniques to

the treatment of serious disturbances of rhythm in patients with seriously compromised ventricular function.

The contributors of this conference have gone a long way in highlighting the state of the art and in identifying the directions we need to take to fully capitalize on the potential of improved physiologic understanding, better pharmacologic agents and the application of surgical techniques to the management of disturbances of cardiac rhythm.

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Responsibility for Health

ELSEWHERE IN THIS ISSUE is a report from Altrocchi on the purported success of the People's Republic of China (PRC) in improving that vast nation's health by emphasizing that health is the individual responsibility of each citizen and commune. There seems to be no doubt that considerable has been accomplished, although the evidence and the data are admittedly still limited. Also in this issue are several papers that examine the concept of holistic health as it is developing in the western world. The holistic health concept also places substantial responsibility for health upon the individual person and somewhat upon the community. As is so often the case with the Orient and the Occident, there are both similarities and differences.

It is likely that the similarities are more apt to pertain to truth and the differences are more apt to pertain to method or approach. The truth may be that medical science and technology are inadequate in themselves to assure health, although they may have much to offer when health is impaired—particularly if seriously so. This view seems to have been accepted by the PRC and is beginning to be recognized here, where the emphasis on individual responsibility for health and wellness appears to be growing. However, Eastern and Western approaches are clearly different and reflect the form of government in each of two great nations. In the PRC the approach is essentially dictated by a central government authority. Here, on the other hand, what we are calling the holistic approach is essentially outside the establishment of medicine and health care, although there are beginning to be some important initiatives in both the public and private sectors.

In conclusion, it may be that the responsibility for health is diffused among individual persons, communities of persons, their governments and the medical profession—which, individually and collectively, is the custodian of our knowledge of the science and technology of medicine and health care. If there is to be health for all on this planet this responsibility, diffuse as it is, must be shared among all of these, whatever the political approach. And the medical profession should always be in a role of leadership—*docere*.

—MSMW

Acne—Fact and Folklore

IN THIS ISSUE of the journal, Dr. David A. Whiting presents a Clinical Review of acne.

Acne is no longer a mysterious disease. Much is known about its pathogenesis, especially the roles of sebum and the renowned acne bacillus, Propionibacterium acnes, denizen of the deep recesses of sebaceous follicles.

A multitude of products produced by this organism—chemical toxins, enzymes, activators of the immune system, leukotactic factors and so forth—convert simple comedones into raging, inflammatory lesions ranging from pustules to big, baggy nodules.

Informed physicians (far too few at present, including some backward-looking dermatologists) have powerful resources for curbing the disease. While cure is impossible, the vivid inflammatory lesions which scar the soul and the skin, can be kept under submission until time, in some unknown way, effects its cure.

An elementary knowledge of the way in which the disease evolves is all that is required to select appropriate therapy. Acne is a two-stage process. It begins with a comedo, an impaction of horny cells which distends the follicle, finally protruding through the orifice as a solid, pigmented, cylinder of horn. Preventing comedones from forming stops the disease at its inception and is the ideal prophylactic treatment. Vitamin A acid is a potent topical anticomedonal agent which prevents horny cells from sticking so tightly together, thereby

keeping the follicular canals patent. Salicylic acid is also useful. These are *not* keratinolytic chemicals; they do not, nor can anything else, dissolve keratin *in vivo*. Further, their effect is not due to *peeling*. The latter is a reaction to injury and most of the old-fashioned peelers (phenol, resorcinol, naphthol and the like) are worthless.

The rupture of a comedo spills bacteria, horn, fats and assorted toxins into the dermis provoking a violent inflammatory reaction, literally an abscess. P. acnes is the angry figure in this event. Fortunately, there are drugs (for topical or oral administration) that can neutralize the adverse effects of P. acnes or directly suppress its growth. Benzoyl peroxide is very effective in depopulating anaerobes within the follicle. This plus vitamin A acid make up a winning combination for effectively managing most cases of inflammatory acne. Learning how to use these two drugs will result in therapeutic successes that will gratify physicians and patients alike. Then for more serious cases there are orally given antibiotics such as tetracycline and erythromycin which can be used safely over long periods at doses half those required for soft tissue infections.

Failures are almost always due to failures on the part of physicians (wrong drugs, wrong advice) or, sometimes, to noncompliant patients, often because of inadequate instruction.

Many physicians still do not know that the fogs of folkloric beliefs concerning the cause and relief of acne have really lifted, making rational, clear-minded therapy a reality. Youngsters can be rescued from the burdens of misbeliefs such as the importance of avoiding enjoyable foods (chocolates, nuts, soft drinks), or that the disease is a punishment for bad thoughts or bad actions, social and sexual. Acne is not a psychosomatic disease nor is it due to that favorite old dodge *hormone imbalance*. It is not, except in very rare cases, an endocrinologic disorder and no money should be wasted in futile laboratory studies. Young persons with acne are healthy, eminently so, except for the acne lesions—the suppression of which must be the focus of attack.

Physicians using the very same drugs do not get the same results. Some still think that there have been no real advances in therapy in 50 years. Equally important to the drugs themselves is the doctor *delivery* system. It takes time to answer all the questions and, especially, to dispel false ideas such as the necessity for frequent washing and the use of abrasives to dislodge comedones. These do more harm than good, and washing six to ten times a day injures the skin spared by the disease. Physicians who like and understand youngsters get the best results.

Finally, on the horizon are derivatives of vitamin A which may be administered orally and hold much promise for treating serious acne. These cut down the supply of sebum which fuels the disease. The retinoids, as they are called, also interfere with the formation of comedones.

Acne at last joins the list of human scourges that medical science has brought to bay.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Alcohol and the Elderly

To the Editor: The request seemed innocent enough: Would I be willing to serve as the physician member on a panel to discuss "Alcohol and the Elderly" in a public forum? Of course, my knee-jerk response was to say "yes."

Then misgivings began to set in. Was there really a problem? Would such a forum serve any purpose? Where could I find unbiased information? What if nobody came? Why hold a public forum to investigate the tippling habits of the elderly when there are other groups in our society whose drinking habits could be more deserving of investigation?

In our own profession, for example, the "impaired physician" has certainly taken his lumps. But what about the "impaired lawyer"? The magazine *Barrister,* the official publication of the American Bar Association, reported that close to 30 percent of our nation's lawyers are lushes. The *American School Board Journal* estimates that over 8 percent of our teaching staffs are problem drinkers. It is no secret that Washington, DC, holds the record for the highest per capita intake of alcohol. Not even the Cloth escapes the problem. The National Conference of Catholic Bishops concedes that at least 5 percent of Catholic bishops have a serious drinking problem.

These considerations aside, what is the true status of alcoholism in elderly Americans? Is there really a cause for alarm and, if so, what is being done about it?

I was in for some surprises. A little research showed that, indeed, there is a problem. And, yes, there are some people trying their best to do something about it.

As the life expectancy of Americans continues to increase, there is, obviously, a proportionate increment in the number of senior citizens. As the numbers increase, so do the problems. As we all know, among the penalties of growing old are loss of status, diminished self-image, loneliness, boredom, depression. Little wonder, then, that there is an absolute increase in the use of alcohol as an escape mechanism. It is estimated that perhaps as many as 10 percent of persons over 60 suffer from alcoholism. In nursing homes the problem rate may approach 20 percent.

Unfortunately, the decreased physiologic reserves of elderly persons render them less able to rapidly metabolize alcohol. The ratio of body water versus fat increases with age. Because alcohol is almost completely soluble in water, the same amount of alcohol per pound of body weight consumed by an older person results in higher concentrations in the brain and the blood. The aging body and brain are less able to withstand the ill effects of alcohol because the slower metabolism retards its elimination.

Until very recently, the plight of elderly alcoholics has been given relatively little attention, due, in part, to a cover-up by the family and a disregard by society. The relatives of an elderly inebriate, through shame, try to keep the problem hidden. Society considers an older tippler as a bit ridiculous, a sad, but uncensured figure. Unlike a younger drinker, a senior citizen who overindulges rarely runs into trouble with the law. Nursing homes usually refuse to accept the bibulous oldster.

If I learned nothing else through my participation in this panel on alcohol and the elderly, it was that there is hope in the future. Now a few agencies, and some dedicated individual persons, are trying to bring about a change in these unfair attitudes.

Setting an example is the Queen Nursing Home in Minneapolis where the program is specifically geared to the care and the cure of elderly alcoholics. Several similar projects are underway in California. A study done by the Harvard Medical School showed that carefully controlled group

cocktail hours at geriatric nursing homes resulted in improved morale, and surprisingly, a bettering of cognitive skills.

Serious work is being done by individual investigators. Foremost is Marc A. Schuckit, formerly director of the Alcoholism and Drug Abuse Institute of the University of Washington, and now continuing his in-depth research of the problems of elderly alcoholics at the Veterans Administration Medical Center in San Diego. There is an ever-increasing effort by church workers to deal with these problems, as exemplified by the pioneering work of Father James E. Royce of Seattle University.

It is now evident to me that I as a practicing physician have given too little thought to the enigma of elderly alcoholics. I am sure most of my colleagues will confess to a similar lack of interest or understanding. How many of us have given thought to the drug interactions between alcohol and the medications we prescribe or the over-the-counter items our patients may be using? Haven't most of us taken the easy course of dismissing elderly alcoholics as a minor social problem rather than a medical responsibility?

Alcoholism in the elderly is difficult of diagnosis, often being overlooked as frailty or senility. It may escape detection because it is deliberately hidden or because we are not on the alert for it. But once detected and diagnosed its treatment is highly successful.

Part of the remedy is society's responsibility. As we strive to rid ourselves of racism and sexism, let us also eliminate ageism. For our part as physicians let us sharpen our skills in geriatric care. Medical schools need to teach courses in geriatrics as well as in pediatrics.

And, yes, maybe more public forums on "Alcohol and the Elderly" will help bring the problem out of the closet.

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Inoculation by Bronchoscopy

To the Editor: I would like to add an interesting case report to the cases of serious infectious complications after flexible fiberoptic bronchoscopy, as reported by Drs. Aelony and Finegold in the October 1979 issue of the journal.

In 1974 I saw in consultation a 20-year-old man who had been involved in an automobile accident in Honolulu in 1972. He had suffered fractured femurs and fracture of the large toe, right foot, and fractured ribs. As a result of the fractured ribs, a pneumothorax on the left developed.

He had been admitted to an Armed Forces Hospital in Honolulu, where a tracheotomy was done and chest tubes were placed; bronchoscopy was carried out via a rigid bronchoscope for the pneumothorax and for control of secretions. Ultimately his condition improved and he was discharged.

Seven months after discharge he had been readmitted with a pulmonary infiltration. Bronchoscopy again was done and organisms grew Pseudomonas pseudomallei, which led to the diagnosis of acute melioidosis. This organism is found classically in Southeast Asia, but is not found in the Hawaiian Islands.

At the time there were other patients with this organism in the hospital and they had previously contracted the infection in Southeast Asia, and there was evidence that in another patient in the hospital at this time with this infection, bronchoscopy had been carried out with the same scope.

It can be assumed, therefore, that this represents a case of transmission of an unusual infection via bronschoscopy somewhat different than the more acute infections as defined by Drs. Aelony and Finegold.

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Gonococcal Pharyngeal Infections

To the Editor: Regarding the letter of Michael Sands in the October issue on "Treatment of Gonococcal Pharyngeal Infections in Men," it was not stated whether the population surveyed was heterosexual or homosexual. Perhaps this information is not known.

It is my understanding that gonococcal pharyngitis in men occurs primarily in the homosexual population. I would appreciate his comment.

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* * *

Dr. Sands Replies

To the Editor: The population in the study group were all homosexual men.

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Refer to: Whiting DA: Acne (Clinical Review). West J Med 131: 551-557, Dec 1979

Clinical Review

Acne

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The cause of acne is still obscure, but genetic predisposition, sebaceous overactivity, overgrowth of bacterial flora and exposure to comedogenic substances are all significant factors.

Acne lesions occur mainly in sebaceous follicles, which are characterized by deep follicular canals and large sebaceous glands. The associated seborrhea is not due to a circulatory excess of androgens but may be caused by a local amplification of androgenic activity. This, in turn, may be due to large numbers of androgen receptors and a high concentration of enzymes such as 17β-hydroxysteroid dehydrogenase, within the sebaceous gland itself. Hyperkeratosis of the retention type in the pilary infrainfundibulum obstructs the outflow of sebum and keratin flakes. This favors the proliferation of Propionibacterium acnes which may initiate inflammation in microcomedos and lead to formation of pustules, papules or nodules.

Topical therapy with tretinoin, benzoyl peroxide and antibiotics such as clindamycin is widely used today. Oral tetracyclines and other chemotherapeutic agents remain necessary in severe cases.

ACNE VULGARIS is the most common disorder of the pilosebaceous system. Favoring areas where sebaceous glands are numerous, it usually affects the face and less frequently the back, and very often it is associated with increased oiliness of the skin. Acne is characterized clinically by the appearance of comedones, pustules, papules and nodules, and is easily diagnosed. Most cases run a protracted course with frequent relapses.

Acne usually begins at puberty and affects most teenagers to some degree. On average, it reaches peak severity in girls at 14 years and in boys at 16 years, and most cases improve by the late teens or early 20's. It may persist until the mid-30's and, often, greasy cosmetics aggravate the condition. In some women, acne does not develop until the late teens or early 20's, but in 3 percent of them it develops well before the onset of the other features of puberty.

The clinical course of acne is influenced largely by genetic factors. However, transient relapses before menstrual periods often occur; various exogenous factors of physical and chemical nature may aggravate acne, and masculinizing conditions can also precipitate the disease. Remissions of acne are common after exposure to the sun.

The treatment of acne, although not curative,

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Submitted, revised, April 4, 1979.

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is successful in controlling the disease in most patients. After resolution of the condition, seborrhea and scarring may persist.

Etiology[1]

Genetic factors. Heredity plays an important role in the development of acne, with a family history of acne being present in 70 percent of cases. Acne is almost sure to develop in those whose parents are or have been affected or in those whose twins have the disease.

Endocrine factors. Circulating androgens must be present if acne is to appear. It is well known that the disease does not occur in male castrates but often does so in women with masculinizing tumors. Acne may improve in pregnant women or with the use of the "maxi-pill" (a high-estrogen content oral contraceptive containing 100 μg of mestranol), but often deteriorates in the premenstrual week. Estrogen can suppress sebum formation, but progesterone has no definite effect.

Bacterial infection. Propionibacterium acnes is present in pilosebaceous follicles and may play a major role in the induction of acne pustules. Superinfection with Gram-negative organisms during antibiotic therapy can also complicate the disease.

Physical and chemical factors. A variety of cosmetics, drugs, other chemicals, mechanical factors and certain types of irradiation may be acnegenic.

Stress factors. Although stress has not been shown to cause acne, it can aggravate the condition, possibly by inducing neurotic excoriation.

Diet. Dietary factors have little importance in acne but, occasionally, the intake of certain foods may appear to be associated with a mild flare of the condition.

Weather and environment. Ultraviolet light is beneficial and acne tends to improve slightly in summer, although it can become much worse in hot, humid conditions found in the tropics.

Racial factors. These factors are of little importance although acne seems less common in Japanese people.

Anatomy and Physiology of the Pilosebaceous System

The pilosebaceous system consists of hair follicles and sebaceous glands. The follicles slant to the skin surface and contain hairs deeply rooted in subcutaneous tissue. The sebaceous glands are intradermal with short ducts opening into the upper part of the follicle. Above this level the pilary canal broadens out and is called the infundibulum.

Hair follicles. There are three types of hair follicles on the face.[2] Terminal follicles contain long, thick, stiff beard hairs which fill the pilary canal. The accompanying sebaceous glands are of normal intermediate size, and the infundibula are short and lined with epithelium that is well developed and keratinized and has a normal barrier function. Continuous desquamation of individual cells occurs to prevent obstruction of the follicular orifices.

Vellus follicles are small structures containing soft hairs which are short and thin. The sebaceous glands are small but active. The follicular pores are minute but their patency is maintained. They far outnumber sebaceous follicles and produce appreciable amounts of sebum.

Sebaceous follicles are limited to the face and upper trunk. They are characterized by deep, cavernous follicular canals, wispy hairs, and large sebaceous glands. The terminal fifth of the infundibulum, or acroinfundibulum, is lined with normal squamous epithelium. The internal four fifths, or infrainfundibulum, is lined with a glycogen-rich epithelium. Its granular layer is meager and its thin keratin layer lacks a normal laminated structure. It sloughs readily to form a loose, porous mass of horny detritus in the follicular canal, or sebaceous filament, which permits sebum to flow through it. The patency of the infundibulum is not easily maintained as it lacks rigid terminal hairs that act as wicks for the outward flow of sebum. It is not surprising that most acne lesions occur in sebaceous follicles.

Sebaceous glands. The function of sebaceous glands in humans is unknown. They are found predominantly in the "sniffing" areas.[3(p63)] They are densest on the scalp, forehead, cheeks and chin, less dense on the back and least dense on the extremities. Sebaceous glands are lobulated and divided into acini by septa. A peripheral pool of undifferentiated basal cells lines the acini.[4] Their lipid content is minimal. They may contain considerable amounts of 17β-hydroxysteroid dehydrogenase,[5] an enzyme possibly involved in androgen synthesis.[6] These cells are metabolically active and replace the steady loss of mature cells in the central pool. Mature cells are swollen with lipids and may contain 3β-hydroxysteroid dehy-

drogenase, an enzyme which is possibly involved in a detoxicating pathway for androgens. The cells eventually burst in the center of the acini, releasing lipids and traces of keratin. This process takes three weeks and the sebum reaches the skin surface a week later.[7(p21)] Sebum is a holocrine secretion that flows slowly from the gland into the hair follicle via one or more sebaceous ducts. In young people there is a good correlation between the size of sebaceous glands and secretory activity. Also, the diameter of each skin pore is roughly proportional to the size of the gland.

Pure sebum consists of 60 percent triglycerides, 20 percent wax esters, 10 percent squalene and 10 percent miscellaneous substances. Lipids elaborated by the epidermis contain mainly cholesterol, sterol esters and phospholipids, and make up only 3 percent of the skin surface lipid film on the face, but proportionately more on the limbs. Variable proportions of the triglycerides in sebum are broken down to fatty acids by lipolytic bacteria and yeasts in the sebaceous follicle. Free fatty acids found on the skin surface reflect intrafollicular bacterial activity.

Sebaceous glands have no nerve supply and are under hormonal control. Their activity is mediated by androgens from the testes, ovaries and adrenal glands. Androgens may be metabolized differently in sebaceous glands to enhance their effects. For example, serum-transport testosterone is converted by 5α-reductase in the skin to 5α-dihydrotestosterone, a more potent stimulator of sebaceous activity. This diffuses through the sebaceous cell membrane into the cytoplasm where it is thought to attach itself to a specific cytosol receptor protein which then transports it to the cell nucleus and retains it there.[8] Prolonged androgenic activity could result in production of messenger RNA causing cytoplasmic biosynthesis of sebum and more androgen receptor protein. In addition, in certain body sites the principal adrenal androgen dehydroepiandrosterone may be converted by 17β-hydroxysteroid dehydrogenase in the undifferentiated sebaceous cell pool to more potent stimulators of sebaceous activity such as dihydrotestosterone and 5α-androstane-3β-17β-diol.[9] Pituitary gonadotrophins may also stimulate sebaceous activity via androgen release from ovaries or testes. Thyroid stimulatory hormone and growth hormone probably act in a permissive way allowing androgens to stimulate sebaceous activity. A pituitary sebrotrophic hormone has been suspected but not proven to occur in humans, although a β-lipotrophin is a possibility.[3(pp152-155)] Estrogens have no effect in physiologic doses but in high doses reduce sebum production 50 percent to 70 percent by suppressing pituitary gonadotrophins. The "maxi-pill" may reduce sebum production by 20 percent to 40 percent. Progesterone has no appreciable effect on sebaceous activity. Adrenal corticosteroids and corticotrophins do not enlarge sebaceous glands.

The acroinfundibulum is colonized by Staphylococcus epidermidis and the lipophilic yeasts, Pityrosporon ovale and P. orbiculare. These are aerobic and have lipolytic activity, but are too superficially located to be of practical importance. Propionibacterium acnes, an anaerobic, Gram-positive diphtheroid colonizes the depths of the infundibulum. It produces lipases, proteases, lecithinase, hyaluronidase and neuraminidase and is itself comedogenic.

The Pathogenesis of Acne

Obstruction of the pilosebaceous canal. Acne is a disease of the sebaceous follicles, and probably originates in those containing sebaceous filaments. There may be an androgen-dependent, inherent defect in the rate of follicular keratinization in acne-prone patients which could lead to the retention-type hyperkeratosis seen in the infrainfundibulum in acne. Initially, the epithelium develops a definite granular layer and lipid accumulates in the epidermal cells. There is also a reduction in the number of keratinosomes (lamellar granules), lysosome-like organelles, which discharge their contents into the intercellular spaces, possibly dissolving the polysaccharide cement there.[10] There is an increased turnover of the follicular epithelium leading to a higher output of horny cells which stick together and do not slough away readily.[11] The follicular canal fills with solid horny detritus and a microcomedo forms which prevents the passage of sebum. The acroinfundibulum is not involved so the follicular orifice does not dilate and remains inconspicuous. This closed comedo gradually enlarges and may take five months to reach 2 mm in diameter and become clearly visible as a whitehead. Closed comedones are the "time-bombs" of acne because they obstruct follicular drainage and eventually rupture to cause inflammatory lesions.[7(p59)] Some gradually transform into open comedones or blackheads which protrude through and dilate the follicular orifice, relieving mechanical obstruction and losing the tendency to

rupture. They are chronic, stable lesions which accumulate keratin, lipid and exfoliated hairs. Their apical black color is due to melanin from the acroinfundibular epithelium.[12] When blackheads are present in excess, inflammatory lesions diminish.

Enlargement of sebaceous follicles. Enlarged sebaceous glands and seborrhea are features of adolescent acne, although serum androgen levels are normal. An end-organ hypersensitivity to androgens is postulated, possibly due to overproduction of testosterone,[13] increased numbers of androgen receptors[14] and increased amounts of 17β-hydroxysteroid dehydrogenase. Higher levels of pituitary sebotrophic hormone, if it exists in humans, may also play a role. The net result is marked sebaceous overactivity which is generally proportionate in severity to the acne.

Changes in skin lipid composition. Triglycerides, wax esters and squalene are increased in acne. Total free fatty acids may be decreased in males but not in females and sebaleic acid is increased in both.[15] Squalene, certain free fatty acids and even wax esters are comedogenic in humans and may lead to early changes in the infrainfundibular epithelium from primary irritation.

Increased bacterial flora. Propionibacterium acnes thrives in comedones and, in addition to splitting triglycerides into free fatty acids, can release other inflammatory mediators like proteases and hyaluronidase. The organism also possesses antigenic properties and can cause immediate and cell-mediated immune reactions which may increase its inflammatory potential. Recent work has shown that at the levels actually present in comedones, free fatty acids are not inflammatory agents in acne, as previously thought.[16,17] It seems likely that important causes of inflammation in acne are the *P. acnes* organisms themselves, as well as insoluble substances such as keratin fragments and hair.

The Evolution of Acne Lesions

Comedo. The dangerous lesions in acne patients are the closed comedones, often at the microcomedo stage which may be invisible. The earliest inflammatory lesion is probably caused by the accumulation of toxic material from bacterial activity. Leukotactic substances diffuse out through the intact follicles and attract neutrophils. These cells cause an intrafollicular abscess which later liquefies and may escape into the dermis, forming a perifollicular abscess.

Pustule (transient papulopustule).[7(pp140-142)] Superficial follicular "blowouts" lead to small elevated lesions which are short-lived. Deeper follicular ruptures cause deep-seated, more chronic lesions. The lesions liquefy often causing the overlying roof to rupture and the comedonal remnants and pus to be discharged onto the skin surface. The breaks in the follicular epithelium are later repaired. This leads to reversion to a sebaceous follicle, or to the formation of secondary comedones, which either become cystic or connect with neighboring lesions to become polyporous. Minimal scarring results.

Papule (nontransient type). More severe inflammation may lead to total collapse of the comedo and destruction of most of the follicular lining. Surface rupture is exceptional and usually lipids, horny detritus and hairs escape into the dermis and form foreign-body granulomas, which may take weeks or months to resolve. Obvious scarring is the final result.

Nodule. Here, there is total disintegration of one or more comedones with the formation of large abscesses involving neighboring follicles. The lesions are serous, hemorrhagic and dissect down to the subcutaneous fat, forming necrotic lesions 1 to 3 cm in diameter. Comedonal remnants and hairs in the tissues lead to foreign-body reactions. Healing takes months and gross scarring results.

Draining sinus. This results from a nodular lesion in which remnants of follicular epithelium survive and form interconnecting tunnels, lined with hyperplastic epithelium. Large, tender lesions are formed which periodically drain and then crust over. Acute and foreign-body type inflammatory changes occur. Again, scarring is inevitable.

Types of Acne Vulgaris

Comedonal acne. This is the mildest type of acne vulgaris, in which whiteheads and blackheads predominate, with minimal inflammatory lesions.

Papulopustular acne. This is a mixture of relatively few comedones with many inflammatory lesions, both superficial and deep.

Acne conglobata. This is the most severe and chronic form of acne in which inflamed nodular and draining lesions predominate and few primary comedones are seen, although secondary come-

dones are often formed. It occurs mainly in white males with severe seborrhea, is worst on the trunk and even involves buttocks and thighs.

Classification of the Acnes[7(p223)]

True acne. Varieties of acne vulgaris include premenstrual acne, menopausal acne, neonatal acne, pyoderma faciale, acne fulminans, acne tropicalis, masculinizing syndromes, acne mechanica and Gram-negative folliculitis. Varieties of acne venenata due to external agents include acne cosmetica, pomade acne, chloracne, oil and tar acne, detergent acne and acne aestivalis. Varieties of comedonal acne due to physical agents include comedones in aging skin and comedones from ionizing radiation.

Acneform eruptions. These are follicular reactions starting with inflammatory changes. Comedones are rare. Causes include iodides, bromides, isoniazid, corticosteroids and corticotrophin, diphenylhydantoin and phenobarbitone.

Acne neonatorum may affect neonates for a short while due to maternal or fetal androgens. Infantile acne occurs later, lasts longer, and may be due to a transient increase in gonadal testosterone.

Pyoderma faciale or explosive postadolescent facial acne of females affects women in their 20's and 30's who have a history of recent major, emotional trauma. It resembles acne conglobata on the face with inflamed lesions which are tender and purplish. It is heralded by severe seborrhea.

Acne fulminans, a rapidly progressing severe and widespread acne with painful ulcerative lesions filled with gelatinous material, occurs most frequently on the trunk. Comedones are rare. There are associated findings such as fever, leucocytosis, a raised sedimentation rate, anemia and polyarthritis.

Gram-negative folliculitis sometimes occurs during long-term treatment of acne with antibiotics. Resistant Gram-negative bacilli colonize the anterior nares and spread out to cause pustules (Enterobacter and Klebsiella) or nodules (Proteus).

Acne cosmetica affects women 20 to 50 years old, usually on the chin and checks. It is caused by foundation creams, night creams, moisturizers, sunscreens and other cosmetics that contain comedogenic substances.

Treatment of Acne Vulgaris

There is no definite cure for acne. Therapy is aimed at keeping the condition under reasonable control and trying to prevent the severe flares that lead to scarring. Therefore, treatment is often necessary for prolonged periods until, eventually, spontaneous resolution occurs.

General Scheme of Treatment

Comedonal acne. Topical exfoliants such as benzoyl peroxide, retinoic acid and salicylic acid are sufficient. Comedo extraction is helpful cosmetically.

Papulopustular acne. Topical exfoliants and oral and topical antibiotics will control most cases.

Acne conglobata. Exfoliants, oral and topical antibiotics and dapsone may help. Sometimes systemic corticosteroids may be required as well. Carefully controlled radiation therapy can benefit selected cases, but must be used with great caution. Despite the current controversy about the risk of thyroid neoplasms, the evidence supporting this possibility seems insufficient to exclude every patient from this method of treatment.[18]

Specific Forms of Treatment

Exfoliants. These may either have comedolytic effects which retard the formation of new comedones as well as quickening the shrinkage of these already formed or have counterirritant effects which increase blood supply and shorten healing time. Retinoic acid or tretinoin, available as a gel, cream or lotion, is an effective comedolytic agent.[19] It interferes with comedo formation by reducing corneocyte adhesion. It also intensifies follicular epithelial proliferation and turnover, thereby assisting in loosening and expelling the comedones. It thins follicular epithelium and renders it more permeable to toxins that may leak through and cause lesions to rupture externally, and also stimulates increased blood flow. It may cause stinging, burning, redness and peeling, and treatment must be started with caution. It also causes a transient outcrop of pustules after three to four weeks in a third of cases. Side-effects often induce patients to abandon therapy but, generally, these improve within two months in those who persevere. Long-term treatment is usually needed to maintain a beneficial effect. However, retinoic acid increases skin susceptibility to sunlight, and its possible influence on the incidence of sun-induced skin cancer is currently under investigation. It should, therefore, be used with great caution in patients exposed to excessive

sun, wind or cold, as well as in those with a genetic predisposition towards undue sun-damage and skin cancer.

Benzoyl peroxide in a stable gel form, preferably alcohol-based, is a useful exfoliant that is also bacteriostatic, which enhances its value. It is available in 5 percent and 10 percent concentrations. It, too, has to be used with caution until the patient can tolerate it. It works well on its own, but if comedones predominate may be used in conjunction with retinoic acid—one being used in the morning and the other at night. Miscellaneous exfoliants are available and salicylic acid 5 percent or 10 percent in 85 percent ethanol and 15 percent propylene glycol is also effective. Elemental sulfur still has its supporters though others condemn it when used alone. Abrasive soaps and sponges are not comedolytic but may help scour away papulopustular lesions. Ultraviolet light increases blood supply and helps resolve inflammatory lesions. Cryotherapy also helps to clear inflamed lesions and may be useful in the treatment of shallow scars.

Antibiotics and chemotherapeutic agents. To eradicate Propionibacterium acnes effectively these agents have to achieve adequate concentrations in the pilosebaceous follicles. Orally given tetracyclines have this ability and long-term, low-dosage tetracyclines have been the mainstay of acne therapy for years. Side-effects are mild and include mild gastrointestinal upsets and candidiasis. These drugs are contraindicated in treating children below eight years, in pregnant women and in patients with renal disease. They lead to the development of resistant Gram-negative commensals which become R-factor carriers. They do not produce serious consequences but may lead to Gram-negative folliculitis. Another useful drug for treating acne is erythromycin. Clindamycin is extremely effective but occasionally causes pseudomembranous colitis. It is active topically and local application twice per day is sufficient.[20] A suitable lotion consists of 600 mg of clindamycin dissolved in 48 ml of 70 percent isopropyl alcohol, 6 ml of water and 6 ml of propylene glycol. Clindamycin is currently under trial to establish its safety as a topical agent. Safe alternatives include erythromycin or tetracycline in a hydroalcoholic vehicle.

Cotrimoxazole (combination of trimethoprim and sulfamethoxazole) can be extremely useful in patients who have become refractory to tetracycline and erythromycin. It may be given in small dosages of 1 to 2 tablets each day for up to three months. In severe cases, dapsone in a dosage of 100 to 150 mg per day may be useful if given with tetracycline for two to three months. Patients given long-term dapsone or cotrimoxazole should have periodic checks of the peripheral white blood cells because both have been reported to cause neutropenia. Neither of these drugs is listed by the FDA as being indicated for acne, so caution in their use is appropriate. Orally given zinc may be effective in the treatment of acne,[21] but larger trials are required to confirm this, as its value is disputed.[22]

Reduction of sebum output. One course of x-ray therapy limited to a total of 1,000 to 1,200 rads can produce a temporary decrease in sebum production of up to 80 percent. It may still be indicated in occasional severe and refractory cases but its possible carcinogenic effects must be borne in mind and shielding of the neck is essential. To produce a substantial decrease in sebum output, estrogens usually have to be given in high doses and unacceptable side-effects result. The "maxi-pill" may be beneficial in mild cases. Therefore, the search for a suitable antiandrogen which is effective topically continues.

Miscellaneous treatments. Diets, vitamins and psychotherapy have no proved value in the treatment of acne. However, oral 13-cis-retinoic acid, still an experimental drug, may prove to be helpful in treating severe forms of acne.[23] Many of the traditional topical agents are useless and some are harmful. Many oily substances in cosmetics are comedogenic and must be avoided. Topical corticosteroids are contraindicated, although intralesional steroid injections may be helpful, especially for nodulocystic lesions. Sometimes, treatment with systemic corticosteroids is necessary for short periods in fulminating cases of acne.

Acne surgery. Procedures for abscess drainage should be kept to a minimum in scope and size as it is easy to cause unsightly scars. Intralesional steroids, chemosurgery, cryosurgery, plastic surgery and, occasionally, dermabrasion have their place in experienced hands in the treatment of acne scarring. It is better to delay surgical procedures until the acne process is completely controlled. Acne scars often improve considerably with time and may take at least a year to reach their final size and shape. Older scars are less likely to respond to intralesional steroids, and

plastic surgical treatment of individual lesions may be of considerable benefit.

REFERENCES

1. Ebling FJ, Rook A: The sebaceous gland, *In* Rook A, Wilkinson DS, Ebling FJG (Eds): Textbook of Dermatology, 2nd Ed, Vol 2. Oxford, Blackwell Scientific Publications, 1972, pp 1545-1546

2. Kligman AM: An overview of acne. J Invest Derm 62:268-287, Mar 1974

3. Cunliffe WJ, Cotterill JA: The Acnes—Clinical Features, Pathogenesis and Treatment. London, WB Saunders Co, 1975

4. Plewig G, Christophers E, Braun-Falco O: Proliferative cells in the human sebaceous gland. Acta Derm Venereol (Stockh) 51:413-422, 1971

5. Calman KC, Muir AV, Milne JA, et al: Survey of the distribution of the steroid dehydrogenases in sebaceous glands of human skin. Br J Derm 82:567-571, Jun 1970

6. Milne JA: Acne vulgaris, *In* Rook A (Ed): Recent Advances in Dermatology, No 3. Edinburgh, Churchill-Livingstone, 1972, p 231

7. Plewig G, Kligman AM: Acne Morphogenesis and Treatment. New York, Springer-Verlag, 1975

8. Adachi K: Receptor proteins for androgen in hamster sebaceous glands. J Invest Derm 62:217-223, Mar 1974

9. Hay JB: A study of the in vitro metabolism of androgens by human scalp and pubic skin. Br J Derm 97:237-246, Sep 1977

10. Knutson D: Ultrastructural observations in acne vulgaris—The normal sebaceous follicle and acne lesions. J Invest Derm 62:288-307, Mar 1974

11. Woo-Sam PC: Cohesion of horny cells during comedo formation—An electron microscope study. Br J Derm 97:609-615, Dec 1977

12. Blair C, Lewis CA: The pigment of comedones. Br J Derm 82:572-583, Jun 1970

13. Sansone G, Reisner RM: Differential rates of conversion of testosterone to dihydrotestosterone in acne and in normal skin—A possible pathogenic factor in acne. J Invest Derm 56:366-372, May 1971

14. Bonne C, Saurate J, Chivot M, et al: Androgen receptor in human skin. Br J Derm 97:501-503, Nov 1977

15. Krakow R, Downing DT, Strauss J, et al: Identification of a fatty acid in human skin surface lipids apparently associated with acne vulgaris. J Invest Derm 61:286-289, Nov 1973

16. Puhvel SM, Sakamoto M: An in vivo evaluation of the inflammatory effect of purified comedonal components in human skin. J Invest Derm 69:401-406, Oct 1977

17. Pye RJ, Meyrick G, Burton JL: Free fatty acids in the early inflammatory papule of acne vulgaris. Clin Exper Derm 2:355-359, Dec 1977

18. Epstein E: Thyroid neoplasm after radiation therapy for acne. Arch Derm 114:1017, Jul 1978

19. Kligman AM, Fulton JE, Plewig G: Topical vitamin A acid in acne vulgaris. Arch Derm 99:469-476, Apr 1969

20. Resh W, Stoughton RB: Topically applied antibiotics in acne vulgaris—Clinical response and suppression of Corynebacterium acnes in open comedones. Arch Derm 112:182-184, Feb 1976

21. Michaelsson G, Juhlin L, Ljunghall K: A double-blind study of the effect of zinc and oxytetracycline in acne vulgaris. Br J Derm 97:561-566, Nov 1977

22. Orris L, Shalita AR, Sibulkin D, et al: Oral zinc therapy of acne. Arch Derm 114:1018-1020, Jul 1978

23. Peck GL, Olsen TG, Yoder FW, et al: Prolonged remissions of cystic and conglobate acne with 13-cis-retinoic acid. N Engl J Med 300:329-333, Feb 1979

Anticipating Arrhythmias

ATTENTION TO DETAIL is all important in cardiac arrhythmias. Find out when your patient has arrhythmias. Sometimes arrhythmias cluster in certain periods of the day. And if that is the case, then you want to tailor your therapy so that the patient gets the maximum therapy before he is apt to have these arrhythmias. If in fact the arrhythmias cluster in the morning or evening, let's say, then organize your therapy around that—and give the patient a larger dose of antiarrhythmic medication an hour or so before the arrhythmias are expected.

—G. CHARLES OLIVER, MD, *St. Louis*

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Informed
OPINION

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Health Care in China—An Individual Responsibility

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Tell the man who remembers that once he was hungry and now he is not, about the individual freedom he has sacrificed; speak of abstract democratic philosophies to those who remember they once were sick and cold and now are well and warm. You speak to the wind.

ROBERT H. MOSER[1]

THOSE INVOLVED in international health following World War II looked forward with optimism to the conquest of the world's major health problems: malnutrition, infectious diseases and overpopulation. Imbued with the Western approach to medical problem-solving, there seemed little doubt that a combination of scientific knowledge, well-trained medical personnel, energy and money could conquer the health problems of the underdeveloped world. Now, however, 30 years later, against a background of antibiotic and pesticide resistance, unforeseen ecologic disasters from dams and other products of Western technology, continued prevalence of undernutrition and serious problems of overpopulation in many parts of the world, skepticism is increasing as to the appropriateness of the Western medical model for less developed countries.

In developed countries, the emphasis has been on the delivery of medical care by highly trained doctor-professionals, armed with a complex and expensive scientific technology, to passive consumer-recipients who seek help when they feel sick. This emphasis on curative rather than preventive medicine, with little attention paid to the social and environmental causes of ill health, has failed to stem the tide of the massive health problems of the less developed nations. Despite the worldwide success in eliminating smallpox, those now involved in international health are seeking new models and more relevant approaches to solving these complex health problems.

It is particularly appropriate, therefore, to study the unique approach of the People's Republic of China which, during the past 25 years, according to the best available reports, appears to have made very impressive and remarkably rapid improvements in the health status of their people. This paper focuses on the new roles of individual Chinese citizens in helping to achieve and maintain higher levels of health.

The Chinese Approach to Health: Brief Background

When the Chinese Communists came to power in 1949, the state of health of their 500,000,000 inhabitants was extremely poor, the result of long-term medical neglect, the war against the Japanese, their own civil war and the ineffectiveness of the Western system of delivering medical care adopted by the Nationalist Chinese Government. Poverty and undernutrition were endemic, tropical and nontropical diseases were chronic and widespread, and frequent epidemic scourges were the rule rather than the exception. Venereal disease, tuberculosis, plague, schistosomiasis,

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typhus, cholera, and other acute and chronic diseases were rampant. Between 30 percent and 40 percent of the children did not survive the first five years of life, and the mortality of infants under the age of a year was about 20 percent.[2] Medical care from physicians was available only to those who could afford it in certain urban centers, where the 10,000 doctors trained in Western medicine were located.[2] Chinese traditional medicine had been outlawed by the Nationalists but continued to function to some degree in rural areas.

Between 1949 and 1965, initial efforts in preventive medicine were made but had little success in overcoming major health problems. With Russian advisors the medical establishment continued to emphasize increased output of technology-oriented physicians, who remained in large urban centers.

Disillusioned by the lack of progress in coping with these massive problems Chairman Mao in 1965 launched the Cultural Revolution, with a major focus on a reorientation of the entire direction of medical education. Western-trained medical leaders were removed from office and political leaders took over control of the new health effort. Medical school training was halved from six years to three years but, more important, a new emphasis was placed on the training of *barefoot doctors* and other types of nonphysician medical personnel. No longer would training in rare and esoteric conditions be tolerated; common health problems were henceforth to receive the entire attention of the health field.[2-7]

The fundamental goals of the Chinese Health System were as follows:

- "Serve the people," with delivery of health care to the long-neglected rural populace which constitutes 80 percent of the Chinese people.
- Emphasize the importance of preventive medicine over curative treatment.
- Legitimize Chinese traditional medicine and its practitioners; analyze the approaches and methods of treatment of both traditional and Western medicine and apply the best of both methods to serving the people.
- Involve each Chinese citizen intimately in his or her own health care and maintenance, and in the health of others.[2,3]

Using these approaches, and backed by the full force of a highly organized totalitarian political ideology, the health status of a quarter of the world's population appears to have improved substantially and dramatically within the past few years.[2,8,9] According to reports released by the Chinese government, and as observed by official visitors to China, the life span has increased from 40 to 70 years; infant mortality levels now rank among the lowest in the world; undernutrition, venereal disease, drug addiction and several of the most devastating epidemic diseases have been virtually wiped out and population growth has slowed significantly.[2,6-8]

Although all relevant data are not yet available and free access to all parts of China has not yet been given to visiting medical delegations, the apparent immense improvement in health status of such a vast population has caught the attention of health planners and social planners all over the world, who seek new solutions to the formidable health problems of the underdeveloped world.

The Chinese Citizen as an Informed Participant in Health Care

In pre-World War II China, peasants and urban workers had little schooling, had no medical knowledge, and were generally unwashed, diseased, undernourished and filled with fatalistic and supernatural explanations for their ill health and miserable condition. A major effort of the People's Republic of China has been to instill in each citizen a sense of personal and social responsibility to participate fully in his own health care and the health of his community. Education, backed by strong political ideology, drives home to each Chinese child and adult that it is the citizen's duty to himself, to his commune and to the state to maintain his own health and that of others, in order to create a viable and productive society that can achieve its stated goals.[2,10]

It is no longer left up to each citizen to decide whether or not he is interested in his own health —it is his *duty* to be healthy in order to be a productive and contributing member of his society. The emphasis is on preventive medicine and the learning of health measures through personal involvement. From the earliest age, modern theories of disease causation and prevention are taught, substituting concepts such as the role of germs and life cycles of parasites for the time-honored folk explanations for disease.

Self-reliance and self-involvement in health matters are emphasized repeatedly. The population learns the importance to themselves and to

the state of personal cleanliness, hygiene, nutrition, proper handling of excrement, early care of disease symptoms, and ways to attack endemic and epidemic disease. Members of each commune and local production teams within these communities are taught self-responsibility for as much of their own health and disease prevention as is locally possible. This includes the vital importance of birth control, sanitation and immunization against a wide variety of diseases such as smallpox, measles, polio, diphtheria, pertussis, tetanus, Japanese B encephalitis, meningitis and tuberculosis.[2,11]

The Citizen's Role in Public Health and Preventive Medicine

Although initial learning about health comes through the school system and by repeated instruction backed by political ideology, the central factor in learning maintenance of health is direct involvement of the entire Chinese populace in health work. This follows a key concept of Chairman Mao, who wrote in 1937 that "All genuine knowledge originates in direct experience."

A fundamental principle of Chinese health ideology is that the mass of Chinese people can overcome any obstacles standing in the way of health. Consequently, large campaigns have been organized and carried out, attacking problems such as drug addiction, venereal disease and several epidemic diseases. In city and country alike, special cleanup days are organized by local health workers and political committees to remove garbage and other refuse and to destroy breeding places for disease-carrying insects and animals. Mass campaigns against pests, such as flies, mosquitoes and rats, are claimed to have eliminated typhus and plague from China and to have decreased the incidence of malaria considerably. A similar *People's War* against snails, using simple yet ingenious methods, has apparently substantially reduced the prevalence of one of the world's most problematic diseases, schistosomiasis—a health problem that has continued to spread in most underdeveloped countries despite years of effort based on scientific technology. Physician-visitors from the West, including medical delegations sent specifically to analyze these claims, are uniformly impressed, although cautioning that all data are not yet freely available.[2,12]

These mass campaigns are inspired and launched by the political leadership, not the medical establishment, but are based nonetheless on scientific study of the best methods of attacking endemic and epidemic diseases in China. Insecticides and other technologic methods of Western medicine are rarely used. Thus, China, using its great numbers of people, combined with straightforward ecologic approaches, appears to have avoided the frequent complications of Western technology when misapplied to underdeveloped countries. For example, instead of using agents such as DDT against flies and mosquitoes or molluscicides against snails—to all of which these organisms can rapidly become resistant—the Chinese use simple techniques such as elimination of breeding areas, distribution of fly swatters and burying of snails with shovelled dirt. Dramatic reduction in the incidence of disease appears to have occurred and, by using such natural methods to control disease, no ecologic disasters appear to have ensued. By launching such campaigns during the slack agricultural season, no essential time is lost from production.[2] As pointed out by the Chinese leadership, the beneficial effects of such campaigns often become immediately apparent to citizen-participants, thus engendering enthusiasm for further campaigns. Such health-related efforts also enhance the strong community feelings being developed by the Chinese ideology and reinforce the political tenets of self-responsibility and "serving the people."[2,8]

The Citizen as Patient

In Western society, an individual person can be unhealthy by his or her choice as long as that ill health is not transmittable to others or does not directly infringe on the rights of others. In China, good health is a duty, not only to one's self, but also to one's local production team and to the state.

When a person becomes ill in China, the full force of the medical and political systems combined is mustered to help him "struggle against his own disease." While health teams use both modern and traditional medical procedures to cure physical or mental diseases, patients receive encouragement and motivation toward *wellness* by studying the ideology of Chairman Mao, reinforced by hospital-based political health workers.[2,9,11]

In addition, a Chinese patient usually receives a detailed explanation of his medical problem by members of the health team who are coequals with him not only in his fight against disease but in society as well. No status barriers of class, pro-

fessionalism or technical language inhibit the interchange, and the patient is encouraged to participate actively in making decisions about his own care. The attention given to each patient, coupled with medical efforts and his own motivation to do his duty and get well for the social and productive good of his commune and his society, serve as powerful forces toward restoring health.

The Citizen as Advocate

Despite the totalitarian nature of China, it is claimed that individual Chinese citizens are encouraged at all levels to participate in the development and realization of the short-range and long-range goals of Chinese society. Political meetings, lectures, films, posters and radio talks repeatedly emphasize the value of participation and the important contribution that individual persons and local production units can make by sharing their creative ideas with each other.[2,9-11] Therefore, although citizens are forced or pressured to become immunized, practice personal and communal hygiene, and use birth control methods, theoretically each has a voice in the approaches to health care carried out in his or her community. An attempt is made by the state to engender within an individual consumer a feeling of participation in his own health care, although there are obvious constraints in a consumer's potential advocacy role in any authoritarian state. Once again, limited access allowed to visiting medical delegations prevents drawing definite conclusions about this aspect of China's approach to health.

The Citizen as Provider

A fundamental concept of Chinese health ideology, and a major reason for their outstanding medical success, is the belief that knowledge of health practices and delivery of medical care should not be the sole province of a highly trained medical elite, but should be widely distributed so that all may benefit. To implement this tenet, the Chinese government has established levels of delivery of health care and preventive medicine based on the minimal knowledge necessary for each stage, to be furthered by direct experience and life-long training.

More than a million barefoot doctors are now distributed throughout rural China, selected from the peasant population and trained for three to six months in preventive medicine and medical care of the most common diseases of their respective communes.[2,9,13,14] Instruction includes methods of traditional and Western medicine—herbs, acupuncture and other folk remedies are used in combination with stethoscopes, blood pressure cuffs, physical examinations and modern medications. The barefoot doctors then return to their communes where they continue to follow their agricultural pursuits as well as delivering medical care and providing instruction in health education and preventive medicine. The barefoot doctors, in turn, train local health workers to aid in environmental sanitation and measures of preventive medicine. Each health worker and barefoot doctor is a fully accepted member of his or her commune who understands local cultural and medical problems; consequently, there is no barrier between consumer and provider.

The training of barefoot doctors is continued through life, not only by direct experience, but also by weekly or monthly visits to local commune and district hospitals. Mobile health teams also visit the communes to offer further instruction to the rural doctors. Any medical problem that cannot be handled on one level is passed to a higher one until the appropriate quality of medical care can be given.

Worker doctors, the equivalent in factories of barefoot doctors, provide first aid for injuries and common minor medical afflictions, and stress to urban workers the importance of individual responsibility for health maintenance and preventive medicine. In urban neighborhoods, *red medical workers*—usually housewives—are trained to insure that their neighbors are properly immunized and instructed in the importance and techniques of birth control. Instructional materials are provided and lectures given in birth control methods, late marriage is encouraged, free abortions are readily available and indirect pressure is applied by keeping monthly records of the type of contraceptive measures being used by each woman of childbearing age.[2,4,5,8]

The effective decentralization of the delivery of medical care and the demystification of the science and art of medicine, have not only led to a rapid distribution of adequate medical care for the 800 million Chinese people, most of whom entirely lacked medical care in the past, but have also provided levels of medical care appropriate for the variety of conditions being treated.[2,4,5,7] Thus, minor disorders, injuries and diseases are treated on the spot by co-workers and friends in their role as barefoot doctors—using herbs, acu-

puncture, moxibustion, personal and community support and political-ideological encouragement. More complex conditions are passed on to commune hospitals, district hospitals or modern urban medical centers where treatment ranks with the best in the world.

Conclusion

It seems clear that many of the major world health problems are not improving satisfactorily in response to Western medical technological methods. Population growth, undernourishment, infectious and parasitic diseases, and the provision of adequate water supply and sewage disposal still represent huge and difficult problems for those involved in international health—and the solutions often appear less attainable now than three decades ago. A key question is whether the formidable health problems of underdeveloped nations can be conquered without more widespread involvement of the citizens themselves. New concepts and approaches are clearly needed if these challenges are to be met.

Irrespective of one's own political outlook or medical orientation, it seems apparent that remarkable achievements have occurred in medical care and basic health maintenance in the People's Republic of China during the past 25 years. The Chinese approach has used a unique blend of political ideology, widespread health education, emphasis on preventive medicine and *wellness,* participation of the entire populace in health care and maintenance through decentralization of medical care delivery, and mass attacks on endemic and epidemic diseases. In a few short years the Chinese appear to have reduced significantly the incidence of major diseases, impressively lowered infant mortality while simultaneously achieving population control, and provided adequate food and medical care to a quarter of the world's population.

Lacking both full access to all pertinent data and the ability to visit all parts of China, it is prudent to withhold final conclusions regarding the Chinese approach to health. However, if their accomplishments are as stated, and no visiting medical delegation has yet been able to deny that, it would appear not only expedient but mandatory to reassess the relevance of Western medicine's doctor-oriented, passive-consumer, high-technology approach to the world's health problems and to scrutinize carefully the Chinese system regarding its applicability to the increasingly complex health problems of the underdeveloped world.

REFERENCES

1. Moser RH: Message From China (Editorial). JAMA 230: 1566-1568, Dec 16, 1974

2. Sidel VW, Sidel R: Serve the People. New York, Josiah Macy, Jr., Foundation, 1973.

3. Sidel VW, Sidel R: The delivery of medical care in China. Sci Am 230:19-27, Apr 1974

4. Sidel V: The barefoot doctors of the People's Republic of China. N Engl J Med 286:1292-1300, 1972

5. Sidel V: Some observations on the health services in the People's Republic of China. Intern J Health Services 2:385-395, 1972

6. Wegman M, Lin T, Purcell E: Public Health in the People's Republic of China. New York, Josiah Macy, Jr., Foundation, 1973

7. Jain KK: The Amazing Story of Health Care in New China. Emmaus, PA, Rodale Press Inc, 1973

8. Sidel V: Medical care in the People's Republic of China. Arch Intern Med 135:916-926, 1975

9. Wilenski P: The Delivery of Health Service in the People's Republic of China. Ottawa, Canada, Inter Develop Res Centre, 1976

10. Gibson G: Chinese medical practice and the thoughts of Chairman Mao. Social Sci Med 6:67-93, 1972

11. Liang MH, Eichling MT, Fine LJ, et al: Chinese health care: Determinants of the system. Am J Pub Health 63:102-110, 1973

12. Basch PF, Bruce JI, Bueding E, et al: Report of the American schistosomiasis delegation to the People's Republic of China. Am J Trop Med Hyg 26:427-454, 1977

13. Smith J: Barefoot doctors and the medical pyramid. Br Med J 2:429-432, 1974

14. Galston WW, Savage JS: Daily Life in People's China. New York, Thomas Y. Crowell Co, 1973

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

HUMANISM AND THE PHYSICIAN—Edmund D. Pellegrino, MD, president of the Catholic University of America and professor at Georgetown University; founding editor of the **Journal of Medicine** and director of the Institute on Human Values in Medicine. The University of Tennessee Press, Knoxville, TN (37916), 1979. 248 pages, $15.50.

Edmund Pellegrino is a physician. At present he is the president of Catholic University of America and a professor at Georgetown. He characterizes himself as an academic clinician. As such he is well known to medical philosophy, not so well known, I suppose, to practicing clinicians. I would like to urge all of these clinicians to read this book; it is relevant, challenging and does all of your homework for you.

As the momentum of science nudges against the status quo of morality, ethics, law, economics and other of mankind's credos, society is forced to restructure its values, preserving the things it most cherishes. As a consequence, the respect for individual values is assuming increasing importance in the field of medicine and health care. "Medicine must become increasingly an examined discipline—one critically justified as science and practice." The presuppositions upon which medicine is built (the conceptual basis) must be open to increasing scrutiny. It is this restructuring process that is the focus of Pellegrino's attention in this new and exciting book. For with the increasing demands of advancing medical technology, *medical science* is inevitably drawn into the field. Since science has no values of its own (save the truth of the hypothesis), philosophy must create them. While in the past the question of value was the business of philosophy, he now proposes it is a mutual challenge for both medicine and philosophy to explore each other; to delineate, define and expand the impact of modern health care on values in the nexus of personal constraints and choices that encompass physician, patient, hospital and health care system—in short, to explore the conceptual basis of health care.

The word *humanism* was intentionally selected for the title, rather than philosophy or ethics, because it more clearly focuses on the growing concern that medicine is becoming *dehumanized*. The word *humanism,* as used here, encompasses "a spirit of sincere concern for the centrality of human values in every aspect of professional activity; the respect for freedom, dignity, worth and the belief systems of individual persons. It implies a sensitive, nonhumiliating and empathetic way of helping with some problems or needs." The human, as differentiated from all other biological forms (plants, lower animals), enters into and is dependent on relationships (and the values emerging from these relationships) for personal integrity. Furthermore, the facilitation or inhibition of the personal values experienced in these relationships drives the biological systems. As such the very fact of human illness, as a human experience, cannot be taken for granted nor demeaned as if it seems only a disturbance of the somatic systems (pathophysiology). The challenge of the mutual work between philosophy and medicine is the fact of human illness as a human experience. Medicine is chosen for it is "the most humane of the sciences and the most scientific of the humanities." The most effective laboratory for this mutual study is the clinical encounter. This he portrays to be a most unusual and unique human relationship. It exists at a juncture between science and the humanities. It is the nexus of choices, options and values.

Pellegrino evokes a compelling mental image, that of the ill person as "wounded humanity." At the one pole of the clinical encounter is the patient who is vulnerable because he experiences the fact of being ill. He is losing the free use of his body, he feels pain, he experiences disability, he lacks knowledge of what is wrong and what to do about it, or how to repair it. Relatively helpless, he is dependent upon the attention and knowledge of others. He is reduced to the role of petitioner, his self-image threatened, his freedom to make decisions limited and the maintenance of his personal values threatened. As such his humanity is *wounded*. At the other pole is the physician in a fiduciary relationship, in that the patient trusts him and expects him to be worthy of the qualities that he professed in a public avowal (the oath), to be competent as a consequence of rigorous training and personal devotion, and to place the well-being of his patient above all else.

Too often in today's health care system this clinical encounter is one of inequality (as such it is unethical). The physician stands as an authority and sole arbiter of what is best. He is subtly coerced in this clinical situation by a number of factors, among which are the following: the increasing democratization of the health care system, the presence of technology which determines its own use, his own value systems which prejudice judgment and are superimposed over the patients, by sub rosa clinical experiments which circumvent consent, and by the fee-for-service payment system which awards the need *to produce* and reduces the patient-person to a consumer. Traditionally the Hippocratic principle supported the physician's role of the responsible one for he was warned to "do no harm." Today, however, even his personal credo is open to question as differences arise over health care requirements in procedures and values among physicians themselves, as well as between medical organizations and society. Note for example the problems engendered by euthanasia, abortion, sterilization, prolongation of life, genetic manipulation and others. These differences are however a modern social and scientific fact, therefore Medicine, especially medical educators and policy makers, needs to rethink and expand the traditional ethical position. Today one strives "to do no harm" to the patient's value system and indeed to help repair the loss of dignity. For "the particular features of illness diminish and obstruct a patient's capacity to live a specifically human existence to its fullest." Moreover, he extends his concern beyond individual physicians and medical schools and includes the hospital as a responsible social organization, not just the sum of its individual members' opinions. He challenges hospitals to evolve their own institutional ethics. He goes one step further; since hospitals are the centers for education in their communities for physicians (seminars, conferences, autopsies, quality assurance and the like) they have a primary responsibility to extend privileges to all physicians to be members of the staff, so that they must remain in touch with the educational and evaluative colloquy.

All of these issues arise from a deep concern for health care in America. As such a subtle caveat emerges:

if Medicine is not aware of, and responsive to, the fine tuning of these ethical concerns, it may be that the coarse tuning of the law will remove all voluntary effort. In that case all lose freedom.

The volume itself is a tribute to both Pellegrino and the University of Tennessee Press. He has skillfully edited this series of former lectures so that there is no redundancy. The book is divided into three main categories and a perfect jewel of an epilogue (straight from the heart) on "To Be a Physician." The categories are (1) Medicine and the Humanities, (2) Humanism and Medical Ethics and (3) Humanistic Medical Education.

The paper is non-shiny, the type large and most readable, the binding strong enough to last "300 years." The bibliography is complete and beautifully arranged; it is totally relevant to the text and as such is liberally annotated. Thus, the reader not familiar with the history of humanistic ideas is at once efficiently educated.

I applaud Pellegrino for his urge to mutual colloquy between philosophy and medicine. His choice of the laboratory of the clinical encounter is a stroke of genius.

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* * *

THE POLITICS OF HEALTH CARE—J. H. U. Brown, PhD, Southwest Research Consortium, San Antonio. Ballinger Publishing Company, 17 Dunster Street, Harvard Square, Cambridge, MA (02138), 1978. 151 pages, $15.00.

After discussing the political forces ("those forces from any section of society that attempt to maintain the status quo or to force change on a system"), the author concludes his brief monograph by raising as many questions about our health care system as he attempts to illuminate. Dr. Brown—researcher, former professor of physiology and close observer of the health system on the national scene—looks at health essentially as a political issue. The political process, he maintains, will decide on the alternatives between private practice or total government control as exemplified in the form of national health insurance; this has been in the debating process for quite some time and the debate appears to be drawing to a close.

The issues and problems he discusses represent no new departure from the considerable amount of literature which confronts, and often assaults, professionals and lay persons alike. But for one who is interested in a cram course review of the data and some of the issues involved in today's debate over national health insurance, this short book represents another contribution toward trying to evaluate, or at least describe, the courses of action under consideration and several programs now in effect. Unfortunately, instead of assuming the role of objective observer in some situations, or presenting the philosophical basis for their underpinning, the author tends to assume the role of advocate and thereby dilutes the impact of some of his presentation. He does, however, raise some very important questions which deserve further study and clarification before final decisions are made.

Brown's view of the health care system is not an optimistic one. His solutions focus primarily on the need for future research and the development of an adequate data base (an endlessly sought goal). He also pleads for "technological assessment of new technology as it develops." He concludes that we do not have a health care system because we have no commitment to national health and there is no purpose or direction for the health care system. He further maintains that we have not yet examined the roles for health care workers and we have not examined the role of technology in the delivery of health services.

Based upon the questions he raises and the problems and issues presented in ten brief chapters, the reader is led to conclude that the political issue of national health insurance does not contain the answer to our current problems.

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* * *

USING MARIJUANA IN THE REDUCTION OF NAUSEA ASSOCIATED WITH CHEMOTHERAPY—Roger A. Roffman, Division Head for Research Training, Alcoholism and Drug Abuse Institute, University of Washington, Seattle; with forewords by Frederick R. Appelbaum, MD, and Lawrence M. Halpern, PhD, University of Washington. Murray Publishing Company Inc., 2312 Third Avenue, Seattle (98121), 1979. 48 pages, $1.95 plus 50 cents postage and handling charge (Washington State residents add 11 cents Sales Tax). Quantity prices on request.

This book is thoroughly researched and well written. Its moderate price puts it well within reach of cancer patients and interested family members. The author has written primarily for this particular audience and, with a few exceptions, succeeds in keeping the material at an understandable level.

Health care professionals also will find this book worthwhile. As the author points out, all the answers on this subject are not in at this time, and both patients and professionals should view the information as being the current state of the art. However, things could change dramatically in the future, what with the research being done on the subject.

I would suggest a new title for the book, since the author addresses side effects of both radiation therapy and chemotherapy, and since the chemotherapy discussed is that used specifically for the treatment of malignant disease. A more appropriate title would be "Using Marijuana in the Reduction of Nausea Sometimes Associated with Chemotherapy and Radiation Therapy in the Treatment of Malignant Disease."

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Page, Lot B.
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Schachter, Julius
Schambelan, Morris
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Schaupp, Willis C.
Scheinman, Melvin M.
Schiller, Nelson B.
Schmidt, R. William
Seaman, William E.
Sebastian, Anthony
Selzer, Arthur E.
Shapiro, Howard A.
Sheagren, John N.
Shearn, Martin A.
Sheldon, George F.
Shickman, Martin
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Siperstein, Marvin
Smith, David E.
Smith, W. McFate
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Suter, Emanuel

Tan, Eng
Thomas, William H.
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Turck, Marvin
Tyrrell, J. Blake

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Valentine, William N.
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Vaughan, Thomas R., Jr.
Versteeg, Donna
Von Hoff, Daniel D.
Vyas, Girish N.

Wallerstein, Robert S.
Wands, J. R.
Ward, John R.
Warnock, David
Watts, H. David
Weinstein, Louis
Wilbur, Dwight L.
Williams, Ralph C., Jr.
Williams, Roger

Zvaifler, Nathan J.

AUTHOR INDEX

Adornato, Bruce T., Palo Alto, CA .....(Oct) 334
Aelony, Yossef, Harbor City, CA .....(Oct) 327
Altrocchi, Paul H., Palo Alto, CA .....(Dec) 558
Anderson, Tom, Bethesda, MD .....(Jul) 54
Andreoli, T. E., Houston .....(Nov) 436
Ansari, Ali, Los Angeles .....(Sep) 244
Applegarth, J. Jerrold, San Francisco .....(Jul) 67

Bader, Max, Seattle .....(Jul) 65
Bakir, Farhan, Baghdad, Iraq .....(Sep) 193
Barnett, H. J. M., London, Ontario, Canada .(Jul) 65
Blaisdell, F. William, Sacramento, CA .....(Nov) 355
Bloor, Colin, San Diego .....(Nov) 441
Bluestone, Rodney, Los Angeles .....(Sep) 242
Boice, James B., San Diego .....(Nov) 441
Bolt, Robert J., Sacramento, CA .....(Aug) 140
Bracis, Raymond, Portland, OR .....(Nov) 438
Braunstein, Glenn D., Los Angeles .....
(Nov) 401, (Dec) 522
Bleck, Eugene E., Stanford, CA .....(Aug) 98
Breitman, Gordon, Glendale, CA .....(Jul) 67
Browning, Scott, San Diego .....(Jul) 62
Bruwer, Andre, Tucson, AZ .....(Jul) 66
Buist, A. Sonia, Portland, OR .....(Aug) 114
Bunker, John P., Stanford, CA .....(Dec) 484
Burrows, Benjamin, Tuscon, AZ .....(Aug) 136

Calin, Andrei, Stanford, CA .....(Sep) 205
Carlson, Rick J., Mill Valley, CA .....(Dec) 466
Carson, Stanley N., Martinez, CA .....(Nov) 355
Caughey, George, Stanford, CA .....(Jul) 24
Chlebowski, Rowan T., Torrance, CA .....(Nov) 364
Chopra, Sawtantra K., Los Angeles ..(Jul) 4, (Sep) 196
Cochran, John H., Jr., Denver .....(Aug) 150
Combs, William A., Bend, OR .....(Sep) 247
Commiskey, Joseph, Stanford, CA .....(Jul) 24
Cone, Lawrence A., Rancho Mirage, CA ....(Sep) 256
Constine, Ronald M., Stanford, CA .....(Aug) 98
Conte, John E., Jr., San Francisco .....(Oct) 344
Corkill, Guy, Sacramento, CA .....(Aug) 166
Csongradi, John, Stanford, CA .....(Aug) 98
Culpepper, R. M., Houston .....(Nov) 436

Davajan, Val, Los Angeles .....(Dec) 516
DeCarvalho, Sergio, Bellflower, CA .....(Aug) 159
Duhl, Leonard J., Berkeley, CA .....(Dec) 473

Edwards, David K., San Diego .....(Sep) 219
Edwards, John E., Jr., Torrance, CA .....(Sep) 247
Einhorn, Lawrence H., Indianapolis .....(Jul) 1
Ericksen, Stephen E., Sacramento, CA .....(Aug) 104

Fee, Willard E., Jr., Stanford, CA .....(Aug) 150
Federman, Daniel D., Boston .....(Nov) 411
Finegold, Sydney M., Los Angeles .....(Oct) 327
Forman, Stephen J., Los Angeles .....(Aug) 152
Fox, E. R. W., Coeur d'Alene, ID .....
(Jul) 68, (Aug) 156, (Oct) 334, (Nov) 448, (Dec) 549
Fulop, Milford, Bronx, NY .....(Oct) 321

Gerber, William G., Berkeley, CA .....(Dec) 484
Gerner, Robert H., Los Angeles .....(Aug) 160
Gilman, June A., Los Angeles .....(Sep) 201
Golden, Jeffrey A., San Francisco .....(Sep) 225
Gonzalez, Rolando, San Francisco .....(Dec) 535
Goris, Michael, Stanford, CA .....(Jul) 24
Grover, Robert F., Denver .....(Jul) 53
Guidotti, Tee L., Washington, DC .....(Jul) 70
Guze, Lucien B., Los Angeles .....(Sep) 247

Hahn, Ricardo G., San Francisco .....(Oct) 344
Hammond, William P., Seattle .....(Aug) 92
Hance, Allan, Stanford, CA .....(Jul) 24
Harer, W. Benson, Jr., San Bernardino, CA .(Aug) 162
Harlan, John M., Seattle .....(Aug) 92
Harmon, Wallace M., Fresno, CA .....(Oct) 336
Heffner, John E., Oceanside, CA .....(Aug) 85
Helm, Nicola A., Rancho Mirage, CA .....(Sep) 256
Hirasuna, Jon D., Sacramento, CA .....(Aug) 140
Hollister, Leo E., Palo Alto, CA .....(Aug) 138
Houston, Mark C., Nashville, TN .....(Nov) 449
Hsu, T. H., Baltimore .....(Oct) 270
Hughes, John I., Los Angeles .....(Sep) 244
Hultgren, Herbert N., Palo Alto, CA .....(Jul) 8
Hutchinson, John C., San Francisco .....(Oct) 344

Issa, Nahla, Baghdad, Iraq .....(Sep) 193

Jacobs, Mark D., Providence, RI .....(Oct) 305
Jacobson, Jay A., Salt Lake City .....(Oct) 349
Johnson, B. Lamar, Jr., Los Angeles .....(Sep) 196
Jones, Kenneth Lee, San Diego .....(Oct) 298
Julien, Robert M., Portland, OR .....(Nov) 438

Kasch, James W., Oakland, CA .....(Nov) 448
Katzung, Bertram G., San Francisco .....(Dec) 533
Kellogg, Bonnie, Los Angeles .....(Sep) 201
Kleeman, Charles R., Los Angeles .....
(Oct) 277, (Nov) 373, (Dec) 486
Kleinman, Richard, Stanford, CA .....(Aug) 98
Kletzky, Oscar, Los Angeles .....(Dec) 516
Kligman, Albert M., Philadelphia .....(Dec) 547
Kurman, Robert J., Washington, DC .....(Dec) 526

Lappé, Marc, Sacramento, CA .....(Dec) 475
Lazar, Gary S., Los Angeles .....(Aug) 152
Little, John W., San Francisco .....(Aug) 122
Longmire, William P., Jr., Los Angeles ....(Aug) 158
Lynch, Michael W., Fresno, CA .....(Oct) 336
Lynne-Davies, Patricia, Stanford, CA .....(Jul) 24

Machleder, Herbert I., Los Angeles .....(Jul) 65
Markovitz, Alvin, Los Angeles .....(Dec) 550
Marton, Keith I., Stanford, CA .....(Sep) 179
Mate, Timothy P., San Diego .....(Jul) 59
Maze, Aubrey, Stanford, CA .....(Aug) 150
Menck, Herman R., Los Angeles .....(Nov) 369
Miller, Richard R., Washington, DC .....(Oct) 334
Mohsenifar, Zab, Los Angeles ....(Jul) 4, (Sep) 196
Morton, William E., Portland, OR .....(Oct) 263
Moser, Robert H., Philadelphia .....(Sep) 239

Murphy, James, San Diego .....(Oct) 298
Murtadha, M., Baghdad, Iraq .....(Sep) 193

Nelson, Alan R., Salt Lake City .....(Nov) 451
Nissenson, Allen R., Los Angeles .....(Oct) 277
Nyhan, William L., San Diego ..(Sep) 219, (Oct) 298

Ockner, Robert K., San Francisco .....(Jul) 36
Odell, William D., Torrance, CA (Nov) 401, (Dec) 516
Ostroy, Paul R., Ft. Detrick, Frederick, MD (Oct) 339

Pace, J. Blair, Santa Ana, CA .....(Aug) 158
Palmer, Edward, Lake Oswego, OR .....(Jul) 69
Parker, Charles E., Los Angeles .....(Oct) 324
Parker, Sam, Los Angeles .....(Aug) 157
Patel, Raman, Los Angeles .....(Sep) 244
Pelletier, Kenneth R., Berkeley, CA .....(Dec) 481
Pepitone-Rockwell, Fran, Sacramento, CA ..(Aug) 166
Phillips, Leon A., Seattle .....(Jul) 82
Pinsky, Michael, Stanford, CA .....(Jul) 24
Platia, Edward V., Baltimore .....(Oct) 270
Pomerantz, Leo M., Beverly Hills, CA .....(Dec) 550
Potts, Malcolm, Research Triangle Park, NC (Nov) 455
Preston-Martin, Susan, Los Angeles .....(Nov) 369

Remen, Naomi, San Francisco .....(Dec) 471
Robin, Eugene D., Stanford, CA .....(Jul) 24
Romanoff, Neil E., Rancho Mirage, CA ....(Sep) 256
Rose, Augustus S., Los Angeles .....(Sep) 252
Rosenblatt, Richard, Sacramento, CA .....(Aug) 166
Rubinstein, Jonathan S., Beverly Hills, CA .(Aug) 148
Rudd, Peter, Stanford, CA .....(Sep) 179
Rufner, Deborah, San Diego .....(Sep) 219

Salfen, S. J., Stanford, CA .....(Jul) 24
Samuelson, Cecil O., Jr., Salt Lake City .....(Jul) 57
Sanazaro, Paul J., Berkeley, CA .....(Nov) 433
Sands, Michael, San Francisco .....(Oct) 338
Sargent, Ed, Corvallis, OR .....(Nov) 448
Sayre, Simon A., Los Angeles .....(Jul) 77
Scharschmidt, Bruce, San Francisco .....(Nov) 417
Scheinman, Melvin M., San Francisco .....(Dec) 537
Seibers, Kathy, Portland, OR .....(Nov) 438
Shapiro, Howard A., San Francisco .....(Aug) 158
Shearn, Martin A., Oakland, CA .....(Nov) 440
Shelub, Irwin, Sacramento, CA .....(Aug) 140
Sherman, Samuel R., San Francisco .....(Sep) 256
Simmons, Daniel H., Los Angeles .....(Sep) 196
Skory, Linda, Oakland, CA .....(Nov) 440
Stapleton, F. Bruder, San Diego .....(Sep) 219
Stapleton, Thomas R., Reno, NV .....(Aug) 165
Starr, Grier F., Eugene, OR .....(Oct) 263
Stein, Martin, San Diego .....(Sep) 219
Steinberg, Stephen E., Seattle .....(Aug) 92
Steinberg, Steven M., San Diego .(Jul) 59, (Nov) 449
Stochosky, Barbara, San Bernardino, CA ...(Aug) 143
Stone, Richard A., San Diego .....(Jul) 59
Svihus, Richard H., Oroville, CA .....(Dec) 478
Swerdlin, Aron H. R., San Diego .....(Jul) 59

Taetle, Raymond, San Diego .....(Jul) 62
Terver, Sylvain P., Stanford, CA .....(Aug) 98
Theodore, James, Stanford, CA .....(Jul) 24
Thomas, Arthur N., San Francisco .....(Dec) 539
Thompson, Jesse E., Dallas .....(Nov) 434
Todd, Malcolm C., Long Beach, CA .....(Dec) 464

Ullyot, Daniel J., San Francisco .....(Dec) 540

Van Kessel, Antonius, Stanford, CA .....(Jul) 24
Vargiu, James, San Francisco .....(Dec) 471
Vernon, Stephen E., Los Angeles .....(Sep) 253
Vieweg, W. V. R., San Diego .....(Nov) 441

Wagner, Sheldon L., Corvallis, OR .....(Aug) 156
Wallace, Andrew G., Durham, NC .....(Dec) 544
Warren, Sanford E., San Diego .....(Nov) 441
Watts, Malcolm S. M., San Francisco .....(Dec) 463
Weinberger, Laurence M., Ventura, CA .....(Sep) 251
Weitzman, Richard E., Torrance, CA .....
(Nov) 373, (Dec) 486
West, Irma, Sacramento, CA .....(Oct) 335
Weston, Raymond E., Los Angeles .....(Oct) 277
Whiting, David A., Dallas .....(Dec) 551
Williams, H. James, Salt Lake City .....(Jul) 57
Williams, Stephen D., Indianapolis .....(Jul) 1
Wilson, Miriam G., Los Angeles .....(Sep) 201
White, Thomas T., Seattle .....(Sep) 251
Woolf, Louis I., Vancouver, BC .....(Oct) 324

IN MEMORIAM

Abbott, Steven L., Jul 24, 1978 .....(Aug) 177
Ahrens, Carlyle L., Dec 2, 1978 .....(Oct) 354
Albi, R. William, Mar 12, 1979 .....(Aug) 177
Anderson, Charles M., Feb 12, 1979 .....(Aug) 177
Anderson, Harold T., Dec 2, 1978 .....(Aug) 177
Bagatelos, Anthony P., Aug 21, 1979 .....(Oct) 354
Bell, Dudley Philip, May 5, 1979 .....(Jul) 84
Beutel, Wolfgang W., Jun 1, 1978 .....(Oct) 354
Bolze, Edward, Jr., Apr 20, 1979 .....(Jul) 84
Bonfilio, Victor P., Jul 19, 1979 .....(Oct) 354
Brown, Louise P., Jan 29, 1979 .....(Nov) 462
Campbell, Dwight G., Mar 3, 1979 .....(Jul) 84
Carroll, Kevin J., Jul 14, 1978 .....(Jul) 84
Coker, John Kenner, Jr., Apr 6, 1979 .....(Jul) 84
Cullen, Stuart C., Aug 11, 1979 .....(Oct) 354
DePuy, James L., Jun 1979 .....(Oct) 354
Dewey, Edward B., Mar 1, 1979 .....(Nov) 462
Doyle, Gerald Francis, Sep 14, 1979 .....(Nov) 462
Ermshar, Lloyd G., Nov 4, 1978 .....(Jul) 84
Ervin, Clinton V., Jr., Jun 3, 1979 .....(Aug) 177
Faber, Harold Kniest, Apr 27, 1979 .....(Jul) 84
Fanson, Anne Ethel, Jan 9, 1979 .....(Nov) 462
Fowler, Charles Beebe, Jun 15, 1979 .....(Aug) 177
Frick, Donald J., Jr., Sep 18, 1978 .....(Nov) 462
Friedberger, William, Jul 24, 1978 .....(Nov) 462
Funnell, Arthur B., Jun 1, 1979 .....(Oct) 354
Garman, James E., Dec 28, 1978 .....(Aug) 177
Geistweit, William Henry, Jr., Jun 13, 1979 .(Aug) 177
Graybill, Martin B., Jul 6, 1979 .....(Aug) 177
Gross, Alvin J., Jul 10, 1979 .....(Aug) 177
Haag, Edgar C., Aug 18, 1979 .....(Oct) 354
Hammerly, Fred, Aug 12, 1979 .....(Nov) 462
Hanson, Raulf A., Feb 9, 1979 .....(Nov) 462
Harley, Garth Howland, Mar 25, 1979 .....(Aug) 177
Henney, James E., Feb 10, 1979 .....(Nov) 462
Hesselberg, Erwin H., Jul 8, 1978 .....(Nov) 462
Hill, George, Jul 11, 1979 .....(Aug) 177
Horton, Hammond Spalding, Aug 2, 1979 ..(Oct) 354

Hunter, Harry D., Mar 19, 1979 .....(Aug) 177
Ingle, Wilfred G., Mar 16, 1979 .....(Nov) 462
Jacobson, George, Mar 18, 1979 .....(Aug) 177
Jensen, Joseph E., Sr., Aug 26, 1978 .....(Oct) 354
Johnson, George E., Dec 14, 1978 .....(Aug) 177
Johnson, Helen M., Apr 14, 1979 .....(Jul) 84
Jordan, John H., Jul 19, 1979 .....(Nov) 462
Kepl, Maxwell F., Mar 10, 1979 .....(Aug) 177
Klinefelter, Robert P., Jun 17, 1979 .....(Aug) 177
Klussmann, Hans, Jun 28, 1979 .....(Aug) 177
Koerper, Victor Eugene, Jul 29, 1979 .....(Nov) 462
Kovitz, Louis, Jul 22, 1979 .....(Oct) 354
Krummes, Harry P., Apr 26, 1979 .....(Jul) 84
Lacey, Lloyd E., May 1979 .....(Aug) 178
Larsen, James D., Feb 20, 1979 .....(Aug) 178
Leicester, Katherine Haworth, Jun 10, 1979 .(Aug) 178
Lundquist, Dell T., Mar 17, 1979 .....(Aug) 178
Marlow, Arthur Ashley, Apr 23, 1979 .....(Jul) 84
Miller, Joseph B., Jul 31, 1979 .....(Oct) 354
Mugler, Frederick R., Jun 16, 1979 .....(Oct) 354
Nugent, Maurice W., Aug 26, 1979 .....(Nov) 462
Parrett, Virgil O., Jun 3, 1979 .....(Aug) 178
Paul, Carl J., Sep 4, 1979 .....(Nov) 462
Pike, Catherine C., Aug 20, 1979 .....(Oct) 354
Planting, Purl L., May 17, 1979 .....(Aug) 178
Porter, James Llewellyn, Apr 1, 1979 .....(Jul) 84
Porter, John E., Apr 24, 1979 .....(Jul) 84
Pritchard, Walter, Aug 28, 1978 .....(Aug) 178
Roth, Merall, Jul 1, 1979 .....(Oct) 354
Rudens, Maurice C., Feb 24, 1979 .....(Nov) 462
Schmidt, Otto Ernest Lincoln, Apr 28, 1979 ..(Jul) 84
Shevick, Murray Paul, Jul 28, 1979 .....(Oct) 354
Sudlow, Edward L., Oct 7, 1978 .....(Oct) 354
Taylor, Alexander, Sep 18, 1979 .....(Nov) 462
Thorne, George W., Apr 6, 1979 .....(Nov) 462
Trolan, J. Austin, May 16, 1969 .....(Jul) 84
Walker, Samuel J., Mar 31, 1979 .....(Nov) 462
Warnock, Archibald W., Jun 7, 1979 .....(Aug) 178
Wells, John J., Dec 15, 1978 .....(Jul) 84
Whitmer, Daniel Warren, Jun 21, 1979 ....(Aug) 178
Wilcox, Alfred, May 5, 1979 .....(Jul) 84
Wilhelm, Paul L., Sep 2, 1979 .....(Oct) 354
Woolsey, John Homer, Jun 21, 1979 .....(Aug) 178

SUBJECT INDEX

A

Abortion, see *Changing Attitudes*
[Abortions], see *Prenatal Diagnosis*
Abuse of Diphenoxylate Hydrochloride [Lomotil], see *Deliberate*
Accreditation of Continuing Medical Education (Editorial) .....(Sep) 239
Acne (Clinical Review), David A. Whiting .(Dec) 551
Editorial, Albert M. Kligman .....(Dec) 547
Acne—Fact and Folklore (Editorial), Albert M. Kligman .....(Dec) 547
Adolescent Gynecology, see *Specialty Conferences*
Adolescents, Hirsutism in, see *Specialty Conferences*
Adriamycin (Doxorubicin) Cardiotoxicity: A Review, Rowan T. Chlebowski .....(Nov) 364
Adult, Still Disease in, see *Leukoerythroblastic Reaction*
Adults, see *Shigellosis in*
Advances in Clinical Medicine, see *Epitomes*
Advertising, see *On Smoking and*
Agricultural Chemicals, see *Safety*
[Airway Obstruction], see *Epiglottitis*
Alcohol and the Elderly (Correspondence), E. R. W. Fox .....(Dec) 549
Alcoholic Hypoglycemia and Ketosis (Editorial), Milford Fulop .....(Oct) 321
Alcoholics, see *Hypoglycemic Coma*
Allergy, Important Advances in, see *Epitomes*
[Alternative Energy], see *Health Implications*
[AMA], see *Accreditation of Continuing Medical Education*
Amenorrhea, Primary, see *Specialty Conferences*
Amenorrhea, Secondary, see *Specialty Conferences*
Amniocentesis, see *Prenatal Diagnosis*
Amyloidosis and Periodic Peritonitis, Farhan Bakir, M. Murtadha, Nahla Issa .....(Sep) 193
Anesthesiology, Important Advances in, see *Epitomes*
[Animal] Bite, see *Meningitis*
Another View of Functional Overlay (Correspondence), Lawrence W. Weinberger ....(Sep) 251
Antidepressants, see *More Effective Use*
Antidepressant Drug Treatment, see *Recent Advances*
Antihypertensive Management, see *Nontraditional Problems*
Arachnidism, see *Necrotic*
Arginine Vasopressin Secretion, see *Clinical Physiology of Water Metabolism, Part I*
Arrhythmias, see *Treatment of Cardiac*
Arthritis, see *Psoriatic*

Articles to Read in Other Journals .....(Aug) 171

Asbestos-Related Lung Disease (Medical Staff Conference) .....(Sep) 225
Aseptic Meningitis in SLE, see *Ibuprofen-Associated*
[Aspirin and Sulfinpyrazone], see *Canadian Cooperative*
Athletic Heart Revisited—Sudden Death of a 28-Year-Old Athlete, Sanford E. Warren, James B. Boice, Colin Bloor, W. V. R. Vieweg ....(Nov) 441
Attitudes Toward Abortion, see *Changing*
Audit Studies, Patient Care, see *Generic Screening*
Audits, see *Patient Care*

B

Bacterial Endocarditis, see *Extracardiac Manifestations*
Bacterial Meningitis in Washington State (Public Health), Paul R. Ostroy .....(Oct) 339
Bite, Dog, see *Meningitis*
Board of Medical Quality Assurance, California's, see *Holistic Care and*

Book Reviews:

Adoption Triangle, The, *Sorosky et al* .....(Oct) 353
Annual Review of Neuroscience—1978, *Cowan et al* .....(Aug) 175
Basic Science of Nuclear Medicine, *Parker et al* .....(Aug) 175
Coronary Heart Disease in Young Women, *Oliver* .....(Aug) 172
General Urology—9th Ed., *Smith* .....(Aug) 172
How To Have Intercourse Without Getting Screwed, *Wear & Holmes* .....(Aug) 173

Humanism and the Physician, *Pellegrino* ...(Dec) 563
Parents' Guide to Child Raising, *Austin* ....(Aug) 173
Parents' Medical Manual, *Austin* .....(Aug) 173
Politics of Health Care, *Brown* .....(Dec) 564
Restoration of Motor Function in the Stroke Patient, *Johnstone* .....(Oct) 353
Retrospectroscope—Insights Into Medical Discovery, *Comroe* .....(Aug) 176
Sleep Apnea Syndromes—Kroc Foundation Series Vol. 11, *Guilleminault & Dement* .....(Oct) 353
Survey of Human Diseases, A, *Purtilo* .....(Aug) 174
Systemic Pathology, 2nd Ed.—Vol 3: Alimentary System, *St C. Symmers* .....(Aug) 174
Using Marijuana in the Reduction of Nausea Associated with Chemotherapy, *Roffman* .....(Dec) 564

Breast, Cancer of, see *Tamoxifen*
Bronchoscopy, see *Fiberoptic* and *Inoculation by*
Bronchoscopy, Flexible Fiberoptic, see *Serious Infectious Complications*

C

California [BMQA], see *Holistic Health Care and*
Canadian Cooperative Trial on Platelet-Inhibiting Drugs (Correspondence), H. J. M. Barnett ..(Jul) 65
Reply, Herbert I. Machleder .....(Jul) 65
Cancer, Breast, Metastatic, see *Tamoxifen*
Cancer, Testicular, see *Chemotherapy of Disseminated*
Cancer, Thyroid, see *Epidemiology of*
Candida Pneumonia—Experience with 20 Patients, Zab Mohsenifar, Sawtantra K. Chopra, B. Lamar Johnson, Jr., Daniel H. Simmons .....(Sep) 196
Cardiac Arrhythmias, see *Treatment of*
[Cardiomyopathy, Familial], see *Athletic Heart*
Cardiopulmonary Resuscitation in a University Hospital—An Analysis of Survival and Cost (Health Care Delivery), Ricardo G. Hahn, John C. Hutchinson, John E. Conte, Jr. .....(Oct) 344
Cardiotoxicity, see *Adriamycin*
Caries, Dental, see *Preventing*
Cedars-Sinai Medical Center, Los Angeles, see *Specialty Conferences*
[Cerebrospinal Fluid], see *Technique to Prevent Headaches . . . Lumbar Puncture*
Cerebrovascular Disease, see *New Techniques in Evaluation*
Changing Attitudes Toward Abortion (Controversial Issues in Medicine), Malcolm Potts .....(Nov) 455
Chemicals, see *Safety of Agricultural*
Chemotherapy for Testicular Germ Cell Neoplasms, see *Implications*
Chemotherapy of Disseminated Testicular Cancer, Lawrence H. Einhorn, Stephen D. Williams .(Jul) 1
Editorial, Tom Anderson .....(Jul) 54
Chest Diseases, see *Epitomes*
China, see *VD in* and *Health Care in*
[Chronic Obstructive Pulmonary Disease], see *Routine Spirometric Testing*
Chronic Pulmonary Disease, see *Relative Contributions of Nature*
Cimetidine (Medical Staff Conference) ....(Nov) 417
[Climbers], see *High Altitude Medical Problems*
Clinical Medicine, Advances in, see *Epitomes*
Clinical Physiology of Water Metabolism (Medical Progress), Richard E. Weitzman, Charles R. Kleeman:
Water Homeostasis—Facts and Uncertainties (Editorial), R. M. Culpepper, T. E. Andreoli .(Nov) 436
Part I. The Physiologic Regulation of Arginine Vasopressin Secretion and Thirst .....(Nov) 373
Part II. Renal Mechanisms for Urinary Concentration; Diabetes Insipidus .....(Dec) 486
(Part III to be published in Vol. 132)

Clinical Review:

Acne, David A. Whiting .....(Dec) 551
Editorial, Albert M. Kligman .....(Dec) 547

Clonidine Hydrochloride Withdrawal Complicating Bilateral Nephrectomy, Timothy P. Mate, Aron H. R. Swerdlin, Richard A. Stone, Steven M. Steinberg .....(Jul) 59
Correspondence: Clonidine Withdrawal Fact or Fiction, Mark C. Houston .....(Nov) 449
Reply, Steven M. Steinberg .....(Nov) 450
Coal Use in the Western States, see *Health Implications*
Coma, see *Hypoglycemic*
Community Practice, see *Pain Clinic Model*
Congenital Dislocation of the Hip—Prognostic Implications of Early Diagnosis, Sylvain P. Terver, Ronald M. Constine, John Csongradi, Richard Kleinman, Eugene E. Bleck .....(Aug) 98
Continuing Education: A Medical School Responsibility? (Medical Education), Simon A. Sayre .....(Jul) 77
Continuing Medical Education, see *Accreditation*

Controversial Issues in Medicine:

Changing Attitudes Toward Abortion, Malcolm Potts .....(Nov) 455

[Correction, July Epitomes] An Incorrect Reference (Correspondence), Stephen E. Vernon ...(Sep) 253
Criminal Populations, see *Mania in*

Correspondence:

Alcohol and the Elderly, E. R. W. Fox .....(Dec) 549
Canadian Cooperative Trial on Platelet-Inhibiting Drugs, H. J. M. Barnett .....(Jul) 65
Reply, Herbert I. Machleder .....(Jul) 65
Clonidine Withdrawal—Fact or Fiction, Mark C. Houston .....(Nov) 449
Reply, Steven M. Steinberg .....(Nov) 450
Evidence in Medicine as a Natural Science, Sergio DeCarvalho .....(Aug) 159
Exercise and Neuromuscular Disease, Bruce T. Adornato .....(Oct) 334
Functional Overlay:
Sam Parker .....(Aug) 157
J. Blair Pace .....(Aug) 158
Laurence M. Weinberger .....(Sep) 251
Human Intestinal Parasites in a Farm Community, Michael W. Lynch, Wallace M. Harmon ..(Oct) 336
Incorrect Reference, An, Stephen E. Vernon .(Sep) 253
Inoculation by Bronchoscopy, Alvin Markovitz .....(Dec) 550
Irish Spring Soap [Dermatological Side Effect], Ed Sargent .....(Nov) 448
Of Decibels, 'Highs' and Privacy, E. R. W. Fox .....(Nov) 448

Of Politics, Smoke Screens and Industry,
Edward Palmer .....(Jul) 69
On Smoking and Advertising,
Richard R. Miller .....(Oct) 334
Reply, E. R. W. Fox .....(Oct) 334
Organized Medicine as 'My Doctors,'
Augustus S. Rose .....(Sep) 252
Patient Care Audits:
Gordon Breitman .....(Jul) 67
J. Jerrold Applegarth .....(Jul) 67
Plight of Tithonus, E. R. W. Fox .....(Aug) 156
Preventing Dental Caries in Children,
E. R. W. Fox .....(Jul) 68
Primary Hypertension—A Disease Entity?
James W. Kasch .....(Nov) 448
Removal of Retained Gallstones,
Howard A. Shapiro .....(Aug) 158
Reply, William P. Longmire, Jr. .....(Aug) 158
Reply, Thomas T. White .....(Sep) 251
Safety of Agricultural Chemicals [2,4,5-T],
Sheldon L. Wagner .....(Aug) 156
Correspondence, Irma West .....(Oct) 335
Technique to Prevent Headaches After Diagnostic
Lumbar Puncture, Robert H. Gerner ....(Aug) 160
Thoughts After Three Mile Island [Nuclear Power],
Andre Bruwer .....(Jul) 66
Toxicity of the Herbicide, 2,4,5-T,
Irma West .....(Oct) 335
Treatment of Gonococcal Pharyngeal Infections in
Men, Michael Sands .....(Oct) 338
Correspondence, Leo M. Pomerantz .....(Dec) 550
Reply by Author .....(Dec) 550
VD in China, Max Bader .....(Jul) 65

Cost, see *Cardiopulmonary Resuscitation*
[Costs], see *Skull Radiography*
[Cutaneous] Melanoma, see *Epidemiologic Clues*

D

Death, Sudden, see *Athletic Heart*
Decibels, see *Of*
Deliberate Abuse of Diphenoxylate Hydrochloride
[Lomotil], a Schedule V Narcotic,
Jonathan S. Rubinstein .....(Aug) 148
Dental Caries, see *Preventing*
[Dermatological Side Effect, Miliaral Rash], see
Irish Spring Soap
[DES Exposed Female], see *Specialty Conferences*
Diabetes Insipidus, see
Clinical Physiology of Water Metabolism, Part II
Diagnosis by Amniocentesis, see *Prenatal*
[Diarrhea], see *Shigellosis in Adults*
[Diethyl]stilbestrol Exposure In Utero, see
Specialty Conferences
Difficulties, Diagnostic, see *Shigellosis in Adults*
Diphenoxylate Hydrochloride [Lomotil], see
Deliberate Abuse
Disease, see *Asbestos-Related Lung*
Disease Entity, see *Primary Hypertension*
Disease in Pediatrics, see *Factitious*
Diseases of Phenylalanine Metabolism (Medical
Progress), Charles E. Parker .....(Oct) 285
Editorial, Louis I. Woolf .....(Oct) 324
Dislocation of the Hip, see *Congenital*
Disseminated Testicular Cancer, see *Chemotherapy*
[Diuretic], see *Mannitol*
Dog Bite, see *Meningitis*
Doxorubicin, see *Adriamycin*
[Drug] Abuse of Diphenoxylate Hydrochloride
[Lomotil], see *Deliberate*
[Drug] Heroin Abuse, see *Thrombocytopenia*
Drug Treatment, see
Recent Advances in Antidepressant
Drug-Induced Liver Disease
(Medical Staff Conference) .....(Jul) 36

E

Early Diagnosis, see *Congenital Dislocation . . . Hip*
Edema, Cerebral, see *Mannitol*

Editorials: (General and Scientific)

General:
Accreditation of
Continuing Medical Education .....(Sep) 239
Alternative Methods of Health Care .....(Dec) 544
How Much Freedom Do We Really Have? ..(Aug) 135
Nationalized Health Care—
A Juggernaut in 1981 .....(Oct) 222
New Kind of Melting Pot .....(Sep) 241
Planning for Health Manpower .....(Nov) 435
PSRO, Politics and Quality Assurance,
Paul J. Sanazaro .....(Nov) 433
Responsibility for Health .....(Dec) 547
Some Conceptual and Practical Problems
Facing Medicine .....(Jul) 52
Tel-Med .....(Aug) 137

Scientific:
Acne—Fact and Folklore,
Albert M. Kligman .....(Dec) 547
Alcoholic Hypoglycemia and Ketosis,
Milford Fulop .....(Oct) 321
Implications of Successful Combination Chemotherapy for Testicular Germ Cell Neoplasms,
Tom Anderson .....(Jul) 54
Lessons From Skull Films .....(Jul) 54
More Effective Use of Antidepressants,
Leo E. Hollister .....(Aug) 138
Mount Olympus Revisited, Robert F. Grover .(Jul) 53
New Perspectives in the Treatment of Hypertensive
Patients, Robert H. Moser .....(Sep) 239
Noninvasive Evaluation of Cerebrovascular Disease,
Jesse E. Thompson .....(Nov) 434
Phenylketonuria and Its Variants,
Louis I. Woolf .....(Oct) 324
Rheumatic Disease—A Case of the Soil and the Seed,
Rodney Bluestone .....(Sep) 242
Routine Spirometric Testing and [Chronic Obstructive Pulmonary Disease] COPD,
Benjamin Burrows .....(Aug) 136
Treatment of Cardiac Arrhythmias,
Andrew G. Wallace .....(Dec) 544
Water Homeostasis—Facts and Uncertainties
R. M. Culpepper, T. E. Andreoli .....(Nov) 436

Education, see *Continuing*
Effective Use of Antidepressants, see *More*
Elderly, see *Alcohol and*
[Electrophysiology], see
Treatment of Cardiac Arrhythmias
Endocarditis, see *Extracardiac Manifestations*

Endocrinology and Adolescent Gynecology, see *Specialty Conferences*
Environment, see *Relationship Between Genetics and . . . Rheumatic Diseases*
[Environmental Health], see *Asbestos-Related Disease*

Environmental Health:

Health Implications of Increased Coal Use in the Western States, Tee L. Guidotti .....(Jul) 70

Epidemiologic Clues to Melanoma Etiology, William E. Morton, Grier F. Starr .....(Oct) 263
Epidemiology of Thyroid Cancer in Los Angeles County, Susan Preston-Martin, Herman R. Menck .....(Nov) 369
Epiglottitis in an Immunosuppressed Host, John H. Cochran, Jr., Willard E. Fee, Jr. Aubrey Maze .....(Aug) 150

Epitomes of Progress:

Chest Diseases .....(Jul) 46
Correction .....(Sep) 253
Physical Medicine and Rehabilitation .....(Aug) 130
Correspondence, Exercise and Neuromuscular Disease, Bruce T. Adornato .....(Oct) 334
Anesthesiology .....(Sep) 231
Allergy .....(Oct) 313
Neurosurgery .....(Nov) 426

[Epstein-Barr Virus], see *Severe Neutropenia*
[Eugene, Oregon], see *Epidemiologic Clues*
Evidence in Medicine as a Natural Science (Correspondence), Sergio DeCarvalho ...(Aug) 159
Exercise and Neuromuscular Disease (Correspondence), Bruce T. Adornato ....(Oct) 334
External Otitis, see *Malignant Pseudomonas*
Extracardiac Manifestations of Bacterial Endocarditis, John E. Heffner .....(Aug) 85

F

Factitious Disease in Pediatrics, see *Specialty Conferences*
[Familial Cardiomyopathy], see *Athletic Heart*
[Familial Mediterranean Fever], see *Amyloidosis and Periodic Peritonitis*
Farm Community, see *Human Intestinal Parasites in*
Fiberoptic Bronchoscopy in Diagnosis of Opportunistic Lung Infections—Assessment of Sputa, Washings, Brushings and Biopsy Specimens, Sawtantra K. Chopra, Zab Mohsenifar ....(Jul) 4
Forum, see *Orthodox Medicine, Humanistic Medicine and Holistic Health Care*
[Fuel], see *Health Implications of Increased Coal Use*
Functional Overlay (Correspondence),
Sam Parker .....(Aug) 157
J. Blair Pace .....(Aug) 158
Laurence M. Weinberger .....(Sep) 251

G

[Gastric Acid] Aspiration, see *Pulmonary*
[Gastrointestinal Disease], see *Cimetidine*
Generic Screening—A Systems Approach to Patient Care Audit Studies (Information), Samuel R. Sherman .....(Sep) 256
Genetics, see *Relationship Between . . . Environment and . . . Rheumatic Diseases*
Gonococcal Pharyngeal Infections, see *Treatment*
[Goris Scan], see *Pulmonary Arteriovenous Communications*
Group II J [Pasteurella], see *Meningitis*
Gynecology, Adolescent, see *Specialty Conferences*

H

Harbor-UCLA Medical Center, Torrance, see *Specialty Conference*
Headaches, see *Technique to Prevent*
Healing, see *On . . . the Whole Person,* and *Orthodox Medicine, Humanistic Medicine and Holistic Health Care Forum*
Health, see *Responsibility for*
Health Care, see *Alternative Methods*
Health Care, see *Nationalized*
Health Care, see *Orthodox Medicine, Humanistic Medicine and Holistic Health Care Forum*

Health Care Delivery:

Cardiopulmonary Resuscitation in a University Hospital—An Analysis of Survival and Cost, Ricardo G. Hahn, John C. Hutchinson, John E. Conte, Jr. .....(Oct) 344

Health Care in China—An Individual Responsibility (Informed Opinion), Paul H. Altrocchi ...(Dec) 558
Editorial .....(Dec) 547
Health Implications of Increased Coal Use in the Western States (Environmental Health), Tee L. Guidotti .....(Jul) 70
Health Manpower, see *Planning for*
Heart, see *Athletic*
Herbicide, 2,4,5-T, see *Safety of Agricultural Chemicals,* and *Toxicity of*
Heroin Abuse, see *Thrombocytopenia*
High Altitude Medical Problems (Medical Progress), Herbert N. Hultgren .....(Jul) 8
Editorial, Robert T. Grover .....(Jul) 53
Hip, see *Congenital Dislocation*
Hirsutism in Adolescents, see *Specialty Conferences*
Holistic Health: A Valuable Approach to Medical Care (*in* Orthodox Medicine, Humanistic Medicine and Holistic Health Care Forum), Marc Lappé .....(Dec) 475
Holistic Health and Medicine: A Challenge (*in* Orthodox Medicine, Humanistic Medicine and Health Care Forum), Leonard J. Duhl ...(Dec) 473
Holistic Health Care, see *Orthodox Medicine (etc) Forum*
Holistic Health Care and California's Board of Medical Quality Assurance (*in* Orthodox Medicine, Humanistic Medicine and Holistic Health Care), John P. Bunker, William G. Gerber .....(Dec) 484
Holistic Medicine, see *Orthodox Medicine (etc) Forum*
Holistic Medicine: From Pathology to Prevention (*in* Orthodox Medicine, Humanistic Medicine and Holistic Health Care Forum), Kenneth R. Pelletier .....(Dec) 481

Holism and Reductionism as Perspective in Medicine and Patient Care (*in* Orthodox Medicine, Humanistic Medicine and Holistic Health Care Forum), Rick J. Carlson .....(Dec) 466
Homeostasis, see *Water*
How Much Freedom Do We Really Have? (Editorial) .....(Aug) 135
Human Intestinal Parasites in a Farm Community (Correspondence), Michael W. Lynch, Wallace M. Harmon .....(Oct) 336
Humanistic Medicine, see *Orthodox Medicine (etc) Forum*
Hyperhistaminemia and Peptic Ulcer, Jon D. Hirasuna, Irwin Shelub, Robert J. Bolt ...(Aug) 140
[Hypertension], see *Clonidine Hydrochloride Withdrawal*
[Hypertension], see *Nontraditional Problems*
Hypertension, see *Primary*
Hypertensive Patients, see *New Perspectives in . . . Treatment*
Hypoglycemic Coma With Ketoacidosis in Nondiabetic Alcoholics, Edward V. Platia, T. H. Hsu .....(Oct) 270
Editorial, Milford Fulop .....(Oct) 321
Hypoparathyroidism, see *Specialty Conferences*

I

Ibuprofen-Associated Aseptic Meningitis in Systemic Lupus Erythematosus, Cecil O. Samuelson, Jr., H. James Williams .....(Jul) 57
Immunosuppressed Host, see *Epiglottitis*
Implications of Successful Combination Chemotherapy for Testicular Germ Cell Neoplasms (Editorial), Tom Anderson .....(Jul) 54
Incorrect Reference, An [Correction] (Correspondence), Stephen E. Vernon ...(Sep) 253

In the Forefront:

Tel-Med: A Success Story, W. Benson Harer, Jr. .....(Aug) 162
Editorial .....(Aug) 137

Infections, Lung, see *Fiberoptic Bronchoscopy*
Infectious Mononucleosis, see *Severe Neutropenia*

Information:

Skull Radiography and Professional Liability, Leon A. Phillips .....(Jul) 82
Editorial .....(Jul) 54
Southern Medical Association Meeting in Las Vegas .....(Jul) 83
Mania in Criminal Populations, Thomas R. Stapleton .....(Aug) 165
Pain Clinic Model for Community Practice, Fran Pepitone-Rockwell, Richard Rosenblatt, Guy Corkill .....(Aug) 166
Generic Screening—A Systems Approach to Patient Care Audit Studies, Samuel R. Sherman ..(Sep) 256
Tomoxifen in the Management of Metastatic Cancer of the Breast, Lawrence A. Cone, Neil E. Romanoff, Nicola A. Helm .....(Sep) 258
Shigellosis in Adults—Diagnostic Difficulties and Delays, Jay A. Jacobson .....(Oct) 349

Informed Opinion:

Perceptions on PSRO, Alan R. Nelson .....(Nov) 451
Editorial, Paul J. Sanazaro .....(Nov) 433
Health Care in China—An Individual Responsibilty, Paul H. Altrocchi .....(Dec) 558
Editorial .....(Dec) 547

Inoculation by Bronchoscopy (Correspondence), Alvin Markovitz .....(Dec) 550
Interface: Holistic Health and Traditional Medicine (*in* Orthodox Medicine, Humanistic Medicine and Holistic Health Care Forum), Malcolm C. Todd .....(Dec) 464
Intestinal Parasites, see *Human*
Irish Spring Soap [Dermatological Side Effect] (Correspondence), Ed Sargent .....(Nov) 448

K

Ketoacidosis, see *Hypoglycemic Coma*
Ketosis, see *Alcoholic Hypoglycemia*

L

[Lane County, Oregon], see *Epidemiologic Clues*
[Lesions], see *Acne*
Lessons From Skull Films (Editorial) .....(Jul) 54
Leukoerythroblastic Reaction in Still Disease in an Adult, Gary S. Lazar, Stephen J. Forman .(Aug) 152
Liability, see *Skull Radiography and Professional*
Liver Disease, see *Drug-Induced*
[Lomotil], see *Deliberate Abuse of Diphenoxylate Hydrochloride*
Los Angeles County, see *Epidemiology of Thyroid Cancer*
Lumbar Puncture, see *Technique to Prevent Headaches*
Lung, see *Pulmonary Arteriovenous*, under *Specialty Conferences*
Lung Disease, see *Asbestos-Related*
Lung Infections, see *Fiberoptic Bronchoscopy*
Lupus Erythematosus, see *Ibuprofen-Associated Aseptic Meningitis*

M

Malignant Pseudomonas External Otitis, John E. Edwards, William A. Combs, Lucien B. Guze .....(Sep) 247
Mania in Criminal Populations (Information), Thomas R. Stapleton .....(Aug) 165
Mannitol, Allen R. Nissenson, Raymond E. Weston, Charles R. Kleeman .....(Oct) 277
Maturation and Primary Amenorrhea, see *Specialty Conferences*
Medical Care, see *Orthodox Medicine, Humanistic Medicine and Holistic Health Care Forum*

Medical Education:

Continuing Education: A Medical School Responsibility?, Simon A. Sayre .....(Jul) 77

Medical Education, see *Accreditation of Continuing*
[Medical Information], see *Tel-Med*
Medical Problems, see *High Altitude*

Medical Progress:

High Altitude Medical Problems,
Herbert N. Hultgren .....(Jul) 8
Editorial, Robert F. Grover .....(Jul) 53
Recent Advances in Antidepressant Drug Treatment,
Stephen E. Ericksen .....(Aug) 104
Editorial, Leo E. Hollister .....(Aug) 138
Relationship Between Genetics and Environment in the Pathogenesis of Rheumatic Diseases,
Andrei Calin .....(Sep) 205
Editorial, Rodney Bluestone .....(Sep) 242
Diseases of Phenylalanine Metabolism,
Charles E. Parker .....(Oct) 285
Editorial, Louis I. Woolf .....(Oct) 324
Clinical Physiology of Water Metabolism,
Richard E. Weitzman, Charles R. Kleeman:
Water Homeostasis—Facts and Uncertanties (Editorial), R. M. Culpepper,
T. E. Andreoli .....(Nov) 436
Part I. Physiologic Regulation of Arginine Vasopressin in Secretion and Thirst .....(Nov) 373
Part II: Renal Mechanisms for Urinary Concentration; Diabetes Insipidus .....(Dec) 486
(Part III to be published in Vol. 132)

Medical School, see *Continuing Education*

Medical Staff Conferences:

Drug-Induced Liver Disease, Chief Discussant:
Robert K. Ockner .....(Jul) 36
Pulmonary Aspiration, Chief Discussant:
John W. Little .....(Aug) 122
Asbestos-Related Lung Disease, Chief Discussant:
Jeffrey A. Golden .....(Sep) 225
Vitamin D. Deficient States—Pathophysiology and Treatment, Chief Discussant:
Mark D. Jacobs .....(Oct) 305
Cimetidine, Chief Discussant:
Bruce Scharschmidt .....(Nov) 417
Treatment of Cardiac Arrhythmias, Discussants:
Bertram G. Katzung, Rolando Gonzalez,
Melvin M. Scheinman, Arthur N. Thomas,
Daniel J. Ullyot .....(Dec) 553
Editorial, Andrew G. Wallace .....(Dec) 544

Medicine, see *Organized*
Medicine, see
Some Conceptual and Practical Problems
Medicine, Alternative Methods, see
Orthodox Medicine, (etc) Forum
Medicine, Clinical, Advances in, see *Epitomes*
Medicine, Holistic, see
Orthodox Medicine, (etc) Forum
Medicine, Humanistic, see
Orthodox Medicine, (etc) Forum
Medicine, Orthodox, see
Orthodox Medicine, (etc) Forum
Medicine, Physical, see *Epitomes*
Medicine, Traditional, see
Orthodox Medicine, (etc) Forum
Medicine as a Natural Science, see *Evidence*
Melanoma Etiology, see *Epidemiologic Clues*
Melting Pot, see *New Kind*
Meningitis, see *Bacterial*
Meningitis, see *Ibuprofen-Associated Aseptic*
Meningitis Caused by Group II J Following a Dog Bite, Raymond Bracis, Kathy Seibers,
Robert M. Julien .....(Nov) 438
Metabolism, see *Diseases of Phenylalanine*
Metastatic Cancer of the Breast, see *Tamoxifen*
Metabolism, Water, see *Clinical Physiology of*
[Mexican-Americans] ,see *Human Intestinal Parasites*
[Miliaral Rash], see *Irish Spring Soap*
Model, see *Pain Clinic*
Mononucleosis, see *Severe Neutropenia*
More Effective Use of Antidepressants (Editorial),
Leo E. Hollister .....(Aug) 138
Mount Olympus Revisited (Editorial),
Robert F. Grover .....(Jul) 53
[Mountain Sickness], see *High Altitude*
Myoglobinuric Acute Renal Failure Associated With Phencyclidine [PCP] Abuse, Raman Patel,
Ali Ansari, John I. Hughes .....(Sep) 244

N

Nationalized Health Care—A Juggernaut in 1981 (Editorial) .....(Oct) 322
Nature, see *Relative Contributions*
Narcotic, see *Deliberate Abuse of Diphenoxylate*
Naval Regional Medical Center, San Diego, see
Specialty Conferences
Necrotic Arachnidism [Spider Bite],
Barbara Stochosky .....(Aug) 143
Nephrectomy, see *Clonidine*
Neuromuscular Disease, see *Exercise*
Neurosurgery, Important Advances in, see *Epitomes*
Neutropenia, see *Severe*
New Kind of Melting Pot (Editorial) .....(Sep) 241
New Perspectives in the Treatment of Hypertensive Patients (Editorial), Robert H. Moser ....(Sep) 239
New Techniques in the Evaluation of Cerebrovascular Disease, Stanley N. Carson,
F. William Blaisdell .....(Nov) 355
Editorial, Jesse E. Thompson .....(Nov) 434
Noninvasive Evaluation of Cerebrovascular Disease (Editorial), Jesse E. Thompson .....(Nov) 434
Nontraditional Problems of Antihypertensive Management, Peter Rudd, Keith I. Marton ...(Sep) 179
Editorial, Robert H. Moser .....(Sep) 239
Correspondence, James W. Kasch .....(Nov) 448
[Nuclear Power], see
Thoughts After Three Mile Island
Nurture, see *Relative Contributions*

O

Obstructive Pulmonary Disease, see
Relative Contributions of Nature
[Ocular] Melanoma, see *Epidemiologic Clues*
Of Decibels, 'Highs' and Privacy (Correspondence),
E. R. W. Fox .....(Nov) 448
Of Politics, Smoke Screens and Industry (Correspondence), Edward Palmer .....(Jul) 69
On Healing the Whole Person: A Perspective (*in* Orthodox Medicine, Humanistic Medicine and Holistic Medicine Forum),
Richard H. Svihus .....(Dec) 478
On Smoking and Advertising (Correspondence),
Richard R. Miller .....(Oct) 334
Reply, E. R. W. Fox .....(Oct) 334
[Oregon, Lane County], see *Epidemiologic Clues*
Oregon, University, see *Specialty Conferences*
Organized Medicine as 'My Doctors' (Correspondence), Augustus S. Rose .....(Sep) 252

Orthodox Medicine, Humanistic Medicine and Holistic Health Care—A Forum:

Introduction, Malcolm S. M. Watts .....(Dec) 463
Interface: Holistic Health and Traditional Medicine, Malcolm C. Todd .....(Dec) 464
Holism and Reductionism as Perspective in Medicine and Patient Care, Rick J. Carlson .....(Dec) 466
What is Health For?—Human Priorities in Health Care, James Vargiu, Naomi Remen .....(Dec) 471
Holistic Health and Medicine: A Challenge, Leonard J. Duhl .....(Dec) 473
Holistic Health: A Valuable Approach to Medical Care, Marc Lappé .....(Dec) 475
On Healing the Whole Person: A Perspective, Richard H. Svihus .....(Dec) 478
Holistic Medicine: From Pathology to Prevention, Kenneth R. Pelletier .....(Dec) 481
Holistic Health Care and California's Board of Medical Quality Assurance, John P. Bunker, William G. Gerber .....(Dec) 484
Editorial: Alternative Methods of Health Care .....(Dec) 544
Editorial: Responsibility for Health .....(Dec) 547

(Forum to be continued in next volume)

[Osler Weber-Rendu Syndrome], see *Pulmonary Arteriovenous*
Otitis, see *Pseudomonas External*
Overlay, see *Functional*

P

[Pacemakers, Radiofrequency], see *Treatment of Cardiac*
Pacific Coast Fertility Society, See *Specialty Conferences: Symposium on Adolescent Gynecology and Endocrinology*
Pain Clinic Model for Community Practice (Information), Fran Pepitone-Rockwell, Richard Rosenblatt, Guy Corkill .....(Aug) 166
Parasites, see *Human Intestinal*
[Parathyroid Hormone], see *Hypoparathyroidism*
[Pasteurella] Group II J, see *Meningitis*
Pathogenesis of Rheumatic Diseases, see *Relationship Between Genetics and Environment*
Pathology, from, to Prevention, see *Holistic Medicine*
Patient Care, see *Orthodox Medicine, Humanistic Medicine and Holistic Health Care Forum*
Patient Care Audit Studies, see *Generic Screening*
Patient Care Audits (Correspondence)
Gordon Breitman .....(Jul) 67
J. Jerrold Applegarth .....(Jul) 67
[PCP] Abuse, see *Myoglobinuric Acute Renal*
Pediatrics, see *Factitious Disease in*
People's Republic of China, see *Health Care*
Peptic Ulcer, see *Hyperhistaminemia*
Perceptions on PSRO (Informed Opinion), Alan R. Nelson .....(Nov) 451
Editorial, Paul J. Sanazaro .....(Nov) 433
Periodic Peritonitis, see *Amyloidosis and*
Peritonitis, see *Amyloidosis and Periodic*
Pharyngeal Infections in Men, see *Treatment of Gonococcal*
Phencyclidine [PCP] Abuse, see *Myoglobinuric Renal*
[Phenylketonuria (PKU)], see *Diseases of Phenylalanine Metabolism*
Phenylketonuria and Its Variants (Editorial), Louis I. Woolf .....(Oct) 324
Physical Medicine and Rehabilitation, see *Epitomes*
Physiologic Regulation of Arginine Vasopressin Secretion and Thirst, see *Clinical Physiology of Water Metabolism, Part I*
Physiology of Sexual Maturation and Primary Amenorrhea, see *Specialty Conferences*
[PKU], see *Diseases of Phenylalanine Metabolism*
Planning for Health Manpower (Editorial) ..(Nov) 435
Platelet-Inhibiting Drugs, see *Canadian Cooperative*
Plight of Tithonus (Correspondence), E. R. W. Fox .....(Aug) 156
Pneumonia, see *Candida*
[Pneumonia], see *Pulmonary Aspiration*
Politics, see *PSRO*
Pregnancies, see *Prenatal Diagnosis*
Prenatal Diagnosis by Amniocentesis in 800 Pregnancies, Miriam G. Wilson, June A. Gilman, Bonnie Kellogg .....(Sep) 201
Preventing Dental Caries in Children (Correspondence), E. R. W. Fox .....(Jul) 68
Primary Hypertension—A Disease Entity? (Correspondence), James W. Kasch .....(Nov) 448
Problems Facing Medicine, see *Some Conceptual*
Professional Liability, see *Skull Radiography*
[Professional Standards Review Organization], see *Perceptions on PSRO*
Prognostic Implications, see *Congenital Dislocation*
Progress in Clinical Medicine, see *Epitomes*
Psoriatic Arthritis Induced by Varicella, Linda Skory, Martin A. Shearn .....(Nov) 440
Pseudomonas External Otitis, see *Malignant*
PSRO, see *Perceptions on*
PSRO, Politics and Quality Assurance (Editorial), Paul J. Sanazaro .....(Nov) 433

Public Health:

Bacterial Meningitis in Washington State, Paul R. Ostroy .....(Oct) 339

Pulmonary Arteriovenous Communications in the Lung, see *Specialty Conferences*
Pulmonary Aspiration (Medical Staff Conference) .....(Aug) 122
Pulmonary Disease, see *Relative Contributions of Nature*
[Pulmonary Diseases], see *Candida Pneumonia*
[Pulmonary Edema], see *High Altitude*
Puncture, Lumbar, see *Technique to Prevent Headaches*

Q

Quality Assurance, see *PSRO, Politics and*

R

[Radiation, Nuclear], see *Thoughts After Three Mile Island*
[Radiofrequency Pacemakers], see *Treatment of Arrhythmias*
Radiography, see *Skull*

Recent Advances in Antidepressant Drug Treatment (Medical Progress), Stephen E. Ericksen ..(Aug) 104
Editorial, Leo E. Hollister .....(Aug) 138
Reductionism, see *Holism and*
Rehabilitation, Physical Medicine and, see *Epitomes*
Relationship Between Genetics and Environment in the Pathogenesis of Rheumatic Diseases (Medical Progress), Andrei Calin .....(Sep) 205
Editorial, Rodney Bluestone .....(Sep) 242
Relative Contributions of Nature and Nurture in Chronic Obstructive Pulmonary Disease, see *Specialty Conferences*
Removal of Retained Gallstones (Correspondence), Howard A. Shapiro .....(Aug) 158
Reply, William P. Longmire, Jr. .....(Aug) 158
Reply, Thomas T. White .....(Sep) 251
Renal Failure, see *Myoglobinuric Acute*
Renal Mechanisms for Urinary Concentration; Diabetes Insipidus, see *Clinical Physiology of Water Metabolism, Part II*
Responsibility, Individual, see *Health Care*
Responsibility for Health (Editorial) .....(Dec) 547
Resuscitation, see *Cardiopulmonary*
Rheumatic Disease—A Case of the Soil and the Seed (Editorial), Rodney Bluestone .....(Sep) 242
Routine Spirometric Testing and COPD (Editorial), Benjamin Burrows .....(Aug) 136

S

Safety of Agricultural Chemicals [2,4,5-T] (Correspondence), Sheldon L. Wagner .....(Aug) 156
Correspondence, Irma West .....(Oct) 335
[San Joaquin Valley], see *Human Intestinal Parasites*
Screening, see *Generic*
Secondary Amenorrhea, Hirsutism in Adolescents and the Clinical Consequences of Stilbestrol Exposure *in Utero*, Part II of Symposium on Adolescent Gynecology and Endocrinology, see *Specialty Conferences*
Serious Infectious Complications After Flexible Fiberoptic Bronchoscopy, Yossef Aelony, Sydney M. Finegold .....(Oct) 327
Correspondence, Alvin Markovitz .....(Dec) 550
Severe Neutropenia in Infectious Mononucleosis, William P. Hammond, John M. Harlan, Stephen E. Steinberg .....(Aug) 92
Sexual Maturation, see *Specialty Conferences*
Shigellosis in Adults—Diagnostic Difficulties and Delays (Information), Jay A. Jacobson ...(Oct) 349
[Skin Problems], see *Acne*
Skull Films, see *Lessons From*
Skull Radiography and Professional Liability (Information), Leon A. Phillips .....(Jul) 82
Editorial .....(Jul) 54
Smoking, see *On Smoking*
Soap [Dermatological Side Effect], see *Irish Spring*
Soil, see *Rheumatic Disease*
Some Conceptual and Practical Problems Facing Medicine (Editorial) .....(Jul) 52
Southern Medical Association Meeting in Las Vegas (Information) .....(Jul) 83

Specialty Conferences:

Pulmonary Arteriovenous Communications in the Lung, (Stanford University Pulmonary Rounds), Moderator: Eugene D. Robin, Participants: Joseph Commiskey, Eugene D. Robin, James Theodore, George Caughey, Michael Goris, S. F. Salfen, Allen Hance, Antonius Van Kessel, Patricia Lynne-Davies, Michael Pinsky .....(Jul) 24
Relative Contributions of Nature and Nurture in Chronic Obstructive Pulmonary Disease (University of Oregon, Department of Medicine, Medical Grand Rounds), Discussant: A. Sonia Buist .....(Aug) 114
Editorial, Benjamin Burrows .....(Aug) 136
Factitious Disease in Pediatrics (UC, San Diego, UC Medical Center, San Diego and US Naval Regional Medical Center, San Diego), Participants: Martin Stein, F. Bruder Stapleton, Deborah Rufner, David K. Edwards, William L. Nyhan .....(Sep) 219
Hypoparathyroidism (UC, San Diego, UC Medical Center, San Diego and US Naval Regional Medical Center, San Diego, Pediatric Conference), Participants: Kenneth Lee Jones, James Murphy, William L. Nyhan .....(Oct) 298
Symposium on Adolescent Gynecology and Endocrinology (Harbor-UCLA Medical Center, Torrance, CA, and Cedars-Sinai Medical Center, Los Angeles), Moderators: Glenn D. Braunstein, William D. Odell:
Part I. Physiology of Sexual Maturation and Primary Amenorrhea:
Physiology of Sexual Maturation, William D. Odell .....(Nov) 401
Primary Amenorrhea, Daniel D. Federman .....(Nov) 411
Part II: Secondary Amenorrhea, Hirsutism in Adolescents and the Clinical Consequences of Stilbestrol [DES] Exposure *in Utero:*
Secondary Amenorrhea, Val Davajan, Oscar Kletzky .....(Dec) 516
Hirsutism in Adolescents, Glenn D. Braunstein .....(Dec) 522
Clinical Consequences of Stilbestrol [DES] Exposure *in Utero*, Robert J. Kurman .....(Dec) 526
(Part III to be published in Vol. 132)

[Spider Bite], see *Necrotic Arachnidism*
[Sphincterotomy], see *Removal of Retained Gallstones*
Spirometric Testing and [Chronic Obstructive Pulmonary Disease] COPD, see *Routine*
Stilbestrol Exposure *in Utero*, see *Specialty Conferences*
Still Disease, see *Leukoerythroblastic Reaction*
Stanford University, see *Specialty Conferences*
Sudden Death, see *Athletic Heart*
[Sulfinpyrazone], see *Canadian Cooperative Trial*
Survival, see *Cardiopulmonary Resuscitation*
Symposium on Adolescent Gynecology and Endocrinology, see *Specialty Conferences*
Systemic Lupus Erythematosus, see *Ibuprofen-Associated*
Systems Approach to Audit, see *Generic Screening*

T

2,4,5-T Herbicide, see *Safety of Agricultural Chemicals*, and *Toxicity of*

Tamoxifen in the Management of Metastatic Cancer of the Breast (Information), Lawrence A. Cone, Neil E. Romanoff, Nicola A. Helm .....(Sep) 258
Technique to Prevent Headaches After Diagnostic Lumbar Puncture (Correspondence), Robert H. Gerner .....(Aug) 160
Tel-Med: A Success Story (In the Forefront), W. Benson Harer, Jr. .....(Aug) 162
Editorial .....(Aug) 137
Testicular Cancer, see *Chemotherapy*
Testicular Germ Cell Neoplasms, see *Implications*
Thirst, see *Clinical Physiology of Water Metabolism, Part I*
Three Mile Island [Nuclear Power], Thoughts After (Correspondence), Andre Bruwer .....(Jul) 66
Thrombocytopenia Associated With Intravenous Heroin Abuse, Raymond Taetle, Scott Browning .....(Jul) 62
Thyroid Cancer, see *Epidemiology of*
Tithonus, see *Plight of*
[Toxic Materials], see *Asbestos-Related Lung Disease*
Toxicity of the Herbicide 2,4,5-T (Correspondence), Irma West .....(Oct) 335
Traditional Medicine, see *Interface: Holistic Health and, (Orthodox Medicine, (etc) Forum)*
[Transduodenal Endoscopic Sphincterotomy], see *Removal of Retained Gallstones*
Treatment of Cardiac Arrythmias (Medical Staff Conference) .....(Dec) 533
Editorial, Andrew G. Wallace .....(Dec) 544
Treatment of Gonococcal Pharyngeal Infections in Men (Correspondence), Michael Sands ...(Oct) 338
Correspondence, Leo M. Pomerantz .....(Dec) 550
Reply by Author .....(Dec) 550

U

UC, Davis, see *Pain Clinic*
UC, Los Angeles, see *Specialty Conferences*
UC, San Diego, Medical Center, see *Specialty Conferences*
UC, San Francisco, see *Cardiopulmonary Resuscitation*
UC, San Francisco, see *Medical Staff Conferences*
Ulcer, see *Hyperhistaminemia and Peptic*
University Hospital [UC, San Francisco], see *Cardiopulmonary Resuscitation*
University of Oregon, see *Specialty Conferences*
Urinary Concentration, see *Clinical Physiology of Water Metabolism, Part II*

V

Varicella, see *Psoriatic Arthritis*
Vasopressin Secretion, see *Clinical Physiology of Water Metabolism, Part I*
VD in China (Correspondence), Max Bader ..(Jul) 65
[Venereal Disease], see *Treatment of Gonococcal*
Vitamin D Deficient States—Pathophysiology and Treatment (Medical Staff Conference) ....(Oct) 305

W

Washington State, see *Bacterial Meningitis*
Water Depletion (Hyperosmolar) and Water Excess (Hyposmolar) Syndromes, see *Clinical Physiology of Water Metabolism, Part III, in Volume 132*
Water Homeostasis—Facts and Uncertainties (Editorial), R. M. Culpepper, T. E. Andreoli .....(Nov) 463
Water Metabolism, see *Clinical Physiology of*
Western States, see *Health Implications*
What Is Health For?—Human Priorities in Health Care (*in* Orthodox Medicine, Humanistic Medicine and Holistic Health Care Forum), James Vargiu, Naomi Remen .....(Dec) 471
Whole Person, see *On Healing*, and *Orthodox Medicine (etc) Forum*

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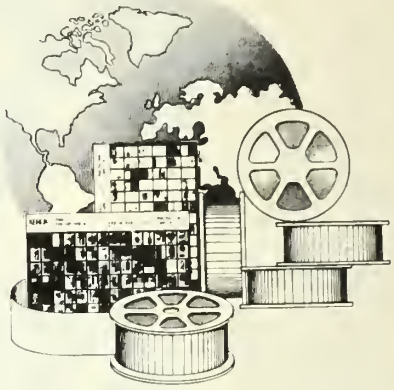

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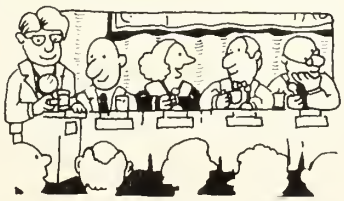

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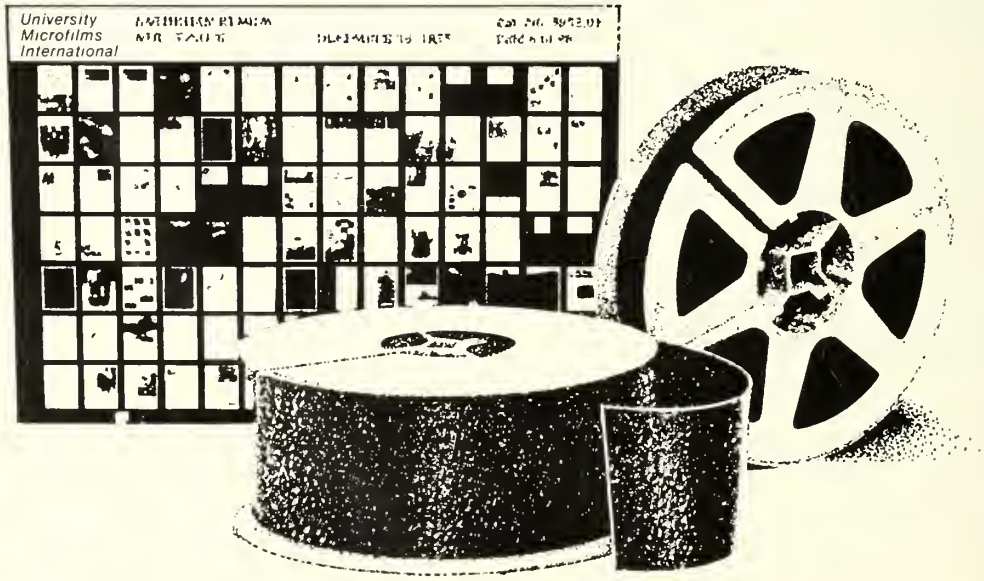

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ANESTHESIOLOGY

January 8-12—**Anesthesia Update.** UCSD at Hotel del Coronado. Tuesday-Saturday. 20 hrs. $200.

January 25-27—**Pediatric Anesthesiology—18th Clinical Conference.** Childrens Hospital at Marriott, Los Angeles. Friday-Sunday. 15 hrs. $160. Contact: Wayne Herbert, MD, P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

February 7-10—**7th Neonatal and Infant Respiratory Symposium.** Ohio State Univ., Dept. of Anesthesiology, at Marriott, Los Angeles. Thursday-Sunday. Contact: John S. McDonald, MD, Dept. of Anesthesiology, OSU, 410 W. 10th Ave., Columbus, OH 43210. (614) 422-5591.

February 13—**Local Anesthesia and Regional Blocks.** See Emergency Medicine, February 13.

March 30-April 5—**Obstetric Anesthesia.** Ohio State University, Dept. of Anesthesiology, at Sheraton Waikiki Hotel, Oahu, Hawaii. One week. Contact: John S. McDonald, MD, Dept. of Anesthesiology, OSU, 410 W. 10th Ave., Columbus, OH 43210. (614) 422-5591.

CANCER

January 7—**The Unknown Primary.** San Joaquin Community Hospital, Bakersfield. Monday. 1 hr. Contact: Oncology Services, San Joaquin Com. Hosp., 2615 Eye St., Bakersfield 93301. (805) 327-1711, ext. 363.

January 16—**Testicular Tumors.** Hospital of the Good Samaritan at Biltmore, Los Angeles. Wednesday. Contact: Janie Sternal, Cont. Med. Ed., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

January 19—**Advances, Treatments and Modern Techniques in Leukemia.** S.F. Regional Cancer Foundation and Leukemia Soc. of America at Fireman's Fund Bldg., San Francisco. Saturday. Contact: Dr. Terry Sheehy, S.F. Reg. Cancer Fndn., 14th and Lake, San Francisco 94118. (415) 211-2132.

January 25-26—**Cancer Update.** Peralta Hospital at Goodman's Hall, Oakland. Friday-Saturday. 10 hrs. Contact: Education and Training Dept., Peralta Hosp., 450 30th St., Oakland 94609. (415) 451-4900.

February 1-3—**Living with Childhood Cancer.** UCSD at Bahia Hotel, San Diego. Friday-Sunday. 14 hrs. $90.

February 23—**Current Trends in Lung Cancer Diagnosis and Management—6th Annual Pulmonary Symposium.** USC and Inter-Community Hosp., Covina, at Calif. State Univ., Pomona. Saturday. 6 hrs. Contact: Linda Arbiter, MPH, Med. Ed. Coordinator, Inter-Community Hosp., 303 N. 3rd Ave., Covina 91723.

March 14—**Cancer of the Endometrium.** California Hospital Medical Center, Los Angeles. Friday. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411, ext. 251.

March 15-16—**Pharmaceutical Aspects of Cancer Care—15th Annual San Francisco Cancer Symposium.** West Coast Cancer Foundation and American Cancer Soc. at Hyatt on Union Square, San Francisco. Saturday-Sunday. Contact: West Coast Cancer Foundation, 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

EMERGENCY MEDICINE

December 15—**Physical Assessment and Diagnosis Course for Emergency and Primary Care Physicians.** Memorial Hospital Medical Center, Long Beach. Saturday. 6 hrs. $65. Contact: Program Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

January 8—**CAT Scan and Ultrasound in Emergency Medicine.** Cottage Hospital and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at Cottage Hosp., Santa Barbara. Tuesday; 8:00 p.m. 1½ hrs. CMA and ACEP. Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

January 14-18—**Medical Management of EMS Systems.** UCSD at Hilton, San Diego, Monday-Friday. 36 hrs.

January 21-25—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Lolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

January 21-25—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

February 11-14—**Emergency Medicine 1980.** UCD at Hyatt Lake Tahoe, Incline Village. Monday-Thursday. 18 hrs. $175.

February 11-15—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

February 13—**Local Anesthesia and Regional Blocks.** Los Robles Hosp. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at Los Robles Reg. Med. Ctr., Thousand Oaks. Wednesday; 8:00 p.m. 1½ hrs. CMA and ACEP. Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

February 14-15—**Maxillofacial Trauma.** See Surgery, February 14-15.

March 9-15—**Mammoth Mountain Emergency Medicine Ski Conference.** UCI and Orange Co. Emergency Dept. Nurses' Assn. at Mammoth Lakes. Sunday-Saturday. 24 hrs. Cat. I CMA, ACEP; 24 elective credit hrs. AAFP. $250. Contact: Daniel Abbott, MD, Med. Conf., Inc., P.O. Box 52-B, Newport Beach 92662. (714) 642-7080.

March 17-21—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

April 12-13—**Symposium on Survival: An Analysis of Disaster Planning.** UCSF. Saturday-Sunday. Contact: UCSF, Cont. Ed. in Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

April 12-19—**Emergency Medicine.** USC at Royal Lahaina, Maui, Hawaii. One week.

April 17—**Infectious Disease for Emergency Physicians.** Goleta Valley Community Hospital and Assn. for Emergency Physicians for Ventura and Santa Barbara Counties at Goleta Valley Hosp., Santa Barbara. Thursday. 1½ hrs. CMA and ACEP. Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

April 21-25—**Postgraduate Institute for Emergency Physicians,** Symposium I. UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

MEDICINE

January 6-13—**Echocardiography in Hawaii.** Honolulu Medical Group Research and Education Foundation, Univ. of Hawaii School of Medicine, Univ. of Rochester School of Medicine at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 18 hrs. Contact: Echocardiography in Hawaii, Honolulu Med. Grp. Research and Ed. Fnd., 550 S. Beretania St., Honolulu 96813. (808) 537-2211.

January 8-12—**Intensive Review of Common Allergic and Asthmatic Diseases.** UCD at Inter-Continental Hotel, Maui, Hawaii. Tuesday-Saturday. 25 hrs. $250.

January 9—**Dermatology Symposium.** N. T. Enloe Memorial Hosp. at Holiday Inn, Chico. Wednesday. 6 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Mem. Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102.

January 9-March 12—**Pulmonary Diseases for the Practicing Internist.** UCLA. Wednesday evenings. 20 hrs.

January 20-24—**Angiography and Vascular Disease.** UCSD at Vacation Village, San Diego. Sunday-Thursday. 26 hrs. $325.

January 26—**Asthma and Allergies.** UCLA. Saturday.

January 26-27—**The Healing Brain.** UCSF Cont. Ed. Health Sciences and Institute for the Study of Human Knowledge at Sheraton-Palace, San Francisco. Saturday-Sunday. Contact: UCSF, Cont. Ed. Health Sciences, 1308 3rd Ave., San Francisco 94143. (415) 666-2894.

January 26-February 2—**Nephrology.** USC at Princeville at Hanalei, Kauai, Hawaii. One week.

January 28-30—**Standards and Controversies in Pulmonary Function Testing: 1980.** Calif. Thoracic Society at Sheraton Harbor Island Hotel, San Diego. Monday-Friday. $250. Contact: Anna B. Roberts, CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

January 31-February 1—**Hypertension: Advances in Treatment.** American Heart Assn., Orange Co. Chap., at Registry Hotel, Irvine. Thursday-Friday. Contact: AHA, Orange Co. Chap., 1043 Civic Center Dr. West, Santa Ana 92703. (714) 547-3001.

January 31-February 2—**Fundamentals of Echocardiography—An Introductory Course for Clinicians.** American College of Cardiology at Century Plaza, Los Angeles. Thursday-Saturday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 1-3—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Bahia Hotel, San Diego. Friday-Sunday. 13 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

February 2—**Pediatric Dermatology Seminar.** STAN. Saturday. Contact: Paul H. Jacobs, MD, Dept. of Derm., Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

February 7-9—**Tri-State Symposium on Clinical Cardiology.** American Heart Assn.'s Council on Clinical Cardiology; AHA, Greater Los Angeles, Arizona and New Mexico Affiliates, at Disneyland Hotel, Anaheim. Thursday-Saturday. 15 hrs. $200, Heart Assn. member; $250, nonmember. Contact: LaVerna Titus, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

February 13—**Chronic Obstructive Pulmonary Disease.** LLU. Wednesday. 4 hrs.

February 13-15—**Advances in Neurology.** UCSF. Wednesday-Friday.

February 13-15—**Cardiovascular Disease—1980: Advances in Diagnosis and Management.** American College of Cardiology at Vacation Village, San Diego. Wednesday-Friday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 16—**5th Annual Liver Conference, Cholestasis.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 7 hrs. $105. Contact: Prog. Coord., Ctr. for Health Ed., 2801 Atlantic Ave, Long Beach 90801. (213) 595-3811.

February 16-17—**Practical Gastroenterology for Primary Care Physicians.** UCLA at Miramar-Sheraton, Santa Monica. Saturday-Sunday. 12 hrs. $160.

February 16-23—**Clinical Allergy.** Univ. of Hawaii, John A. Burns Sch. of Med. at Maui Surf Hotel, Maui, Hawaii. One week. 28 hrs. $250. Contact: Delia M. Chang, Cont. Med. Ed., Univ. of HI, John A. Burns Sch. of Med., 1960 East-West Rd., Honolulu 96822.

February 21-24—**Federation of Western Societies of Neurological Science—Annual Meeting.** Biltmore Hotel, Santa Barbara. Thursday-Sunday. Contact: J. Carroll Ramseyer, MD, EEG/EMG Laboratory, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017.

February 22-23—**Medical Knowledge Self Assessment II.** American College of Physicians and PMC at Hyatt Regency, San Francisco. Friday-Saturday. 12 hrs. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

February 22-23—**Rehabilitation in Neurological Dysfunction.** PMC at Mark Hopkins Hotel, San Francisco. Friday-Saturday. 9 hrs. $135.

March 7—**6th Annual Diabetes Program.** UCD at Red Lion Motor Inn, Sacramento. Friday. 6½ hrs.

March 7-9—**Northern California-Nevada Regional Meeting, American College of Physicians.** Doubletree Inn, Monterey. Friday-Sunday. Contact: Ralph O. Wallerstein, MD, 3838 California St., San Francisco 94118.

March 11-13—**Pulmonary Complications of Trauma.** Alta Bates Hospital, Calif. Society for Respiratory Therapy, American Lung Assn. of Alameda Co. at Hyatt Lake Tahoe, Incline Village. Tuesday-Thursday. 9 hrs. Contact: Claudia F. Read, Medical Ed., Alta Bates Hosp., 3001 Colby, Berkeley 94705. (415) 845-7110, ext. 2031.

March 13-16—**Pediatric Cardiology—A Growing Concern: What the Primary Care Physician Should Know.** UCD at Hyatt Lake Tahoe, Incline Village. Thursday-Sunday. 11 hrs.

March 15-16—**Human Lymphocyte Antigens.** UCSD at Hilton, San Diego. Saturday-Sunday.

March 16-19—**Basic Cardiology for the Primary Care Physician.** UCSF at Yosemite. Sunday-Wednesday.

March 21-23—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Jack Tar Hotel, San Francisco. Friday-Sunday. 15 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

March 24-26—**4th Annual Review and Update of the Immunology and Clinical Practice of Allergy.** USCD at Hilton, San Diego. Monday-Wednesday. 20 hrs. $210.

March 24-April 4—**Intensive Review of Internal Medicine.** USC. Two weeks.

March 26-28—**Endocrine Glands in Health and Disease.** UCSF at Golden Gateway Holiday Inn, San Francisco. Wednesday-Friday.

March 29-April 5—**Infectious Diseases.** Univ. of Washington School of Medicine at Naniloa and Kona Surf Hotels, Hilo, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 7-16—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe. 10 days. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 9—**Cardiovascular Disease.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 7 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Memorial Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 284.

April 9—**Asthma in Childhood.** See Pediatrics, April 9.

April 9-June 11—**Practical Dermatology for the Practicing Internist.** UCLA. 10 Wednesday evenings. 20 hrs.

April 10-13—**Current Concepts and Advances in Diagnosis, Management and Prevention of Cardiac and Cardiopulmonary Diseases.** American Medical Assn. and American College of Cardiology at Los Angeles. Contact: AMA, 535 N. Dearborn, Chicago 60610. (312) 751-6000.

April 12-13—**Pediatric Dermatology.** UCLA. Saturday-Sunday.

April 12-19—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

April 25-27—**New Concepts in Clinical Electrocardiography.** American College of Cardiology at Beverly Hilton Hotel, Beverly Hills. Friday-Sunday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 26-27—**Practical Rheumatology.** UCLA. Saturday-Sunday.

April 28-30—**Pediatric Dermatology.** STAN at Rancho Mirage. Monday-Wednesday. 18 hrs. $195.

OBSTETRICS AND GYNECOLOGY

January 12-19—**Perinatal Medicine.** USC at Royal Lahaina, Maui, Hawaii. One week.

January 20-23—**Obstetrics-Gynecology Update.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Wednesday. 20 hrs.

January 21-25—**Ob/Gyn Review.** USC. Monday-Friday.

January 23-26—**Clinical Obstetrics and Gynecology and Histological Pathology.** UCI and Women's Hospital of Long Beach at Newporter Inn, Newport Beach. Wednesday-Saturday. 26 hrs. $250. Contact: Prog. Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801.

February 9-10—**Obstetrical and Gynecological Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton, Beverly Hills. Saturday-Sunday. 10 hrs. $70. Contact: Miss Dee Davis, Exec. Sec., 5820 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

March 12—**Vaginitis.** LLU. Wednesday. 4 hrs.

March 22-23—**Contraception: Current Research and Multidisciplinary Applications.** See Of Interest To All, March 22-23.

PEDIATRICS

February 2—**Pediatric Dermatology Seminar.** See Medicine, February 2.

February 4-6—**Pediatric Nephrology and Urology.** UCSD at Vacation Village, San Diego. Monday-Wednesday.

February 7-10—**7th Neonatal and Infant Respiratory Symposium.** See Anesthesiology, February 7-10.

February 9-10—**The Health of the Young and the Development of Sexuality and Gender.** UCSF Cont. Ed. Health Sciences at Sheraton-Palace, San Francisco. Saturday-Sunday. Contact: UCSF, Cont. Ed. Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

February 21-23—**Practical Orthopedics for the Pediatrician.** Children's Hospital Medical Center of Northern Calif. at Sahara Tahoe Hotel, South Lake Tahoe. Thursday-Saturday. Contact: Gretchen Hayes, Med. Staff Office, Children's Hosp. Med. Ctr., 51st and Grove Sts., Oakland 94609. (415) 654-5600, ext. 215.

February 23—**Pediatric Review.** UCLA. Saturday.

March 5-7—**Pediatric Pulmonary Symposium.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

March 8—**Adolescent Medicine.** UCLA. Saturday.

March 13-16—**Pediatric Cardiology.** See Medicine, March 13-16.

April 4-5—**Pediatric Topics 1980.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 9 hrs. $80.

April 9—**Asthma in Childhood.** LLU. Wednesday. 4 hrs. $30.

April 11-12—**Pediatric Symposium—22nd Annual.** So. Calif. Permanente Medical Group at Sheraton Hotel, Anaheim. Friday-Saturday. Contact: Shirley Gach, Ed. and Research Dept., SCPMG, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

April 12-13—**Pediatric Dermatology.** See Medicine, April 12-13.

April 28-30—**Pediatric Dermatology.** See Medicine, April 28-30.

PSYCHIATRY

January 12—**Neuroregulators and Brain Function.** No. Calif. Psychiatric Assn. and McAuley Institute at St. Mary's Hosp., San Francisco. Saturday. 3 hrs. Contact: George L. Ponomareff, MD, 2457 Grove Way, Suite 102, Hayward 94546.

January 18-20—**Brief Psychotherapy.** UCSF. Friday-Sunday.

January 26-27—**The Healing Brain.** See Medicine, January 26-27.

January 27-February 1—**Midwinter Program in Continuing Education for Psychiatrists—6th Annual.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday. 26 hrs. $200.

February 2—**Dealing With Depression.** UCLA. Saturday.

February 6-9—**Update in Psychiatry: Psychopharmacology.** UCSD at Vacation Village, San Diego. Wednesday-Saturday. 16 hrs. $200.

February 9—**Childhood Experiences and Adult Behavior.** No. Calif. Psychiatric Assn. and McAuley Institute at St. Mary's

Hosp., San Francisco. Saturday. 3 hrs. Contact: George L. Ponomareff, MD, 2457 Grove Way, Suite 102, Hayward 94546.

February 9-10—**Sexual Therapy.** UCLA. Saturday-Sunday.

March 15—**The Void—Treatment of a Narcissistic Patient.** No. Calif. Psychiatric Society and McAuley Institute at St. Mary's Hospital, San Francisco. Saturday. 3 hrs. $15. Contact: George L. Ponomareff, MD, 2457 Grove Way, Suite 102, Hayward 94546.

March 21-23—**Narcissism—A Multidimensional View.** UCSF. Friday-Sunday.

April 12-13—**Intellect and Illness.** UCLA at Palo Alto. Saturday-Sunday.

RADIOLOGY AND PATHOLOGY

January 9—**Gastrointestinal Radiology and Diagnosis.** LLU. Wednesday. 4 hrs.

January 10—**Bone and Joint Clinical-Pathological-Radiological Correlation Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 23-25—**7th Annual Genitourinary Pathology Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 23-26—**Clinical Obstetrics and Gynecology and Histological Pathology.** See Obstetrics and Gynecology, January 23-26.

January 25-27—**32nd Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Nathan Green, MD, 15107 Vanowen St., Van Nuys 91405.

January 26-27—**Modern Gastrointestinal Radiologic Techniques for Practicing Physicians.** UCSF at Fairmont, San Francisco. Saturday-Sunday. 13 hrs. $200.

January 28-February 1—**Computed Tomography, Ultrasound and X-Ray—An Integrated Approach.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. 32 hrs. $295.

January 30-February 1—**Genito-Urinary Pathology—7th Annual Course.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 22½ hrs. $220. Contact: Prog. Coord., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 1-3—**Neuroradiology.** UCSF at Fairmont, San Francisco. Friday-Sunday. 20 hrs. $190.

February 14—**Bone and Joint Clinical-Pathological-Radiological Correlation Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 22—**Practical Laboratory Mycobacteriology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 27-29—**Sierra Radiology Conference—Radiology of Problems in Clinical Medicine.** Sacramento Radiology Research and Education Foundation and Northern Calif. Radiological Society at Sahara Tahoe Hotel, South Lake Tahoe. Wednesday-Friday. 18 hrs. $215. Contact: Michael H. Reid, PhD, MD, Prog. Dir., Sacramento Radiology Research and Education Foundation, P.O. Box 161112, Sacramento 95816.

March 1-2—**Concepts and Controversies in Cardiopulmonary Imaging.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday. 11 hrs. $150.

March 3-7—**Diagnostic Radiology.** UCSF. Monday-Friday.

March 8-9—**A Practical Course in B-Scan Ultrasound.** UCSF. Saturday-Sunday.

March 13—**Bone and Joint Clinical-Pathological-Radiological Correlation Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 10—**Bone and Joint Clinical-Pathological-Radiological Correlation Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 23 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

January 14-18—**Otologic Surgery Course—15th Annual.** Ear Research Institute, Los Angeles. Monday-Friday. 40 hrs. $500. Contact F. H. Linthicum, Jr., MD, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

January 18-19—**2nd Annual Postgraduate Course in Surgery.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 12 hrs.

January 21-24—**Assembly in Surgery.** UCSD at Islandia Hyatt House, San Diego. Monday-Thursday. 28 hrs.

January 22-June 14—**Recent Advances in Surgical Science.** UCLA at Wadsworth VA Hospital, Los Angeles. One evening/month.

January 27-30—**21st Annual Theodor Billroth Course in Surgical Anatomy.** LLU. Sunday-Wednesday. 32 hrs. $250.

January 31-February 2—**Calculi.** American Urological Assn. at San Francisco. Wednesday-Friday. Contact: Office of Education, AUA, P.O. Box 1129, Aspen, CO 81611. (303) 925-2018.

February 1-3—**National Symposium on Hair Replacement Surgery.** Am. Academy of Facial Plastic and Reconstructive Surgery and Am. Soc. for Dermatologic Surgery at Beverly Hilton Hotel, Beverly Hills. Friday-Sunday. 19 hrs. $475. Contact: AAFPRS, 70 W. Hubbard St., Suite 202, Chicago 60610.

February 6-8—**Glaucoma.** UCSF at St. Francis Hotel, San Francisco. Wednesday-Friday. 16 hrs. $225.

February 7-9—**Vascular Surgery.** UCSF. Thursday-Saturday.

February 8-9—**Cataract Surgery and Intraocular Lenses: Planned Extracapsular, Phacoemulsification and Intracapsular Techniques.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $450. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

February 14-15—**Maxillofacial Trauma.** UCSF at Fairmont Hotel, San Francisco. Thursday-Friday. 15 hrs. $200.

March 1—**Corneal-External Ocular Disease Surgery Course.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $225. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

March 7-8—**Ophthalmology Update.** UCD, PMC, UCSF, STAN. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

March 15-19—**Controversial Areas in Surgery—17th Annual Seminar.** UCLA at Canyon Hotel, Palm Springs. Saturday-Wednesday.

March 18-21—**Basic Science for Surgeons.** STAN at The Lodge, Pebble Beach. Tuesday-Friday.

March 19-23—**Vascular Surgery—8th Annual Symposium.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday.

March 25-29—**3rd U.S. Intraocular Lens Symposium and 7th Scientific Session.** American Intra-Ocular Implant Society at Century Plaza Hotel, Los Angeles. Tuesday-Saturday. 30 hrs. Contact: Debbi Miller, Dir. of Mtg. Services, AIOIS, P.O. Box 3140, Santa Monica 90403. (213) 395-3937.

April 3-4—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

April 11-12—**New Techniques in Hip Resurfacing and Replacement: In-Depth Course and Workshop.** UCLA. Friday-Saturday.

April 18-19—**Workshop on Orthopedic Injuries.** PMC. Friday-Saturday.

April 19-20—**Office Orthopedics/Office Urology.** UCLA. Saturday-Sunday.

April 24-25—**11th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. Contact: Mrs. Lu Hendricks, JSEI, UCLA Sch. of Med., Los Angeles 90024.

April 24-26—**General Surgery.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday.

April 26-May 3—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $290.

OF INTEREST TO ALL PHYSICIANS

December 15—**Physical Assessment and Diagnosis Course for Emergency and Primary Care Physicians.** See Emergency Medicine, December 15.

January 8-March 25—**Acupuncture, Acupressure and Transcutaneous Nerve Stimulation for Pain Control.** UCLA. Tuesday evenings. 58 hrs. $500.

January 11-13—**Great Debates Over Controversies in Management of High Risk Patients.** Cedars-Sinai Med. Ctr. at Century Plaza Hotel, Los Angeles. Friday-Sunday. 19 hrs. Contact: Lori Kahane, Cedars-Sinai Med. Ctr., P.O. Box 48750, Los Angeles 90048. (213) 855-5547.

January 12—**How to Get a Good Night's Sleep.** UCLA. Saturday.

January 12-13—**Current Drugs and Their Usage.** UCLA. Saturday-Sunday. 11 hrs. $150.

January 21-25—**Therapy: Principles and Use of Drugs.** STAN at Hyatt on Union Square, San Francisco. Monday-Friday. 25 hrs. $290.

January 30-February 2—**Primary Care: Current Management of Common Office Problems.** UCSF. Wednesday-Friday.

January 31-February 2—**Medical and Legal Aspects of Asbestosis.** USC. Thursday-Saturday.

February 1-7—**LLU Alumni Association—48th Annual Postgraduate Convention.** One week.

February 4-9—**Family Practice Refresher Course—11th Annual.** UCI at Marriott Inn, Newport Beach. Monday-Saturday.

February 5-June 24—**Family Practice Review.** USC. Tuesday evenings.

February 8-13—**California Medical Association—109th Annual Session.** Town and Country, San Diego. Friday-Wednesday. Contact: Rocki Lai, CMA.

February 9-10—**Sexual Therapy.** See Psychiatry, February 9-10.

February 10-13—**Medical Evaluation of the Preoperative Patient.** UCD at Hyatt Lake Tahoe, Incline Village. 15½ hrs. $135.

February 13—**Environmental Medicine.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 6 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Mem. Mosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 283.

February 13-15—**30th Annual Course for Physicians in Family Practice.** Mt. Zion Hosp. and Med. Ctr., San Francisco. Wednesday-Friday. 20 hrs. Contact: Heidi Benson, Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

February 14-15—**Management of the Ventilator Dependent Patient.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. 14 hrs. Contact: Prog. Coord., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 15-16—**Health Care and the Changing Society.** Vista Hill Foundation and Mesa Vista Hosp. at Hotel del Coronado, Coronado. Friday-Saturday. 9 hrs. Contact: Virginia Everett, Vista Hill Foundation, 3420 Camino del Rio, Suite 100, San Diego 92108. (714) 563-1770.

February 21-22—**New and Old Antibiotics.** USC. Thursday-Friday.

February 21-23—**Musculoskeletal Diagnostics and Treatment—Towards a More Rational Perspective.** American Academy of Physical Medicine and Rehabilitation and Eisenhower Med. Ctr. at Gene Autry Hotel, Palm Springs. Thursday-Saturday. Contact: Paul H. Goodley, MD, Pain Diagnostics and Rehabilitation Institute, 2210 W. 3rd St., Los Angeles 90057. (213) 383-8485.

February 23-24—**Health in the Workplace.** UCSF Cont. Ed. Health Sciences. Saturday-Sunday. Contact: UCSF, Cont. Ed. Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

February 24-26—**Neurology for Non-Neurologists.** UCSD at Hilton, San Diego. Sunday-Tuesday. 21 hrs. $250.

February 25-29—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $290.

February 26-March 2—**Critical Care Medicine.** USC at Hilton, San Francisco. Tuesday-Sunday.

February 27—**Hospital Infection Control.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday. 7 hrs. Contact: Prog. Coord., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

March 1-2—**Genetic Disorders.** UCLA. Saturday-Sunday.

March 5-April 23—**General Preventive Medicine.** USC. Wednesday evenings.

March 9-15—**Critical Care II and Ski.** College of Medical Education, Pierce Co. (WA) Med. Soc. at Sahara Lake Tahoe, Incline Village. One week. Contact: Maxine Bailey, College of Med. Ed., Pierce Co. Med. Soc., 705 S. 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

March 9-16—**Sports Medicine.** Center for Sports Medicine, Northwestern Univ. Med. Sch.; Div. of Sports Med., No. Carolina Dept. of Public Instruction at Intercontinental Hotel, Maui, Hawaii. One week. Contact: Marianne Porter, Ctr. for Sports Med., 2-063, 303 E. Chicago Ave., Chicago 60611.

March 12—**Refresher in Family Practice.** N. T. Enloe Memorial Hosp. at Holiday Inn, Chico. Wednesday. 6 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Mem. Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 283.

March 15—**Medical Treatment of Alcoholism.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7 hrs.

March 15-16—**Practical ENT for Primary Care Physicians.** UCLA. Saturday-Sunday.

March 15-16—**Human Lymphocyte Antigens.** See Medicine, March 15-16.

March 15, 29—**Placebos: The Power of Positive Expectant Faith.** UCLA. 2 Saturdays.

March 18-22—**Sports Medicine.** University of Hawaii School of Medicine at Princess Kaiulani Hotel, Waikiki, Honolulu, Hawaii. Tuesday-Saturday. 18 hrs. $200. Contact: Hawaii Conference Services, P.O. Box 25055, Honolulu 96825. (808) 377-6445.

March 20-23—**4th Annual Basic Clinical Hypnosis Workshop.** UCI at Balboa Bay Club, Newport Beach. Thursday-Sunday.

March 22-23—**Contraception: Current Research and Multidisciplinary Applications.** UCSF. Saturday-Sunday. Contact: UCSF, Cont. Ed. Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

March 24-28—**Postgraduate Institute for Primary Care Physicians.** UCSD at Vacation Village, San Diego. Monday-Friday.

April 7-9—**Clinical Dermatology for the Family Practitioner.** UCD at Ahwahnee Hotel, Yosemite. Monday-Wednesday. 20 hrs.

April 8, 15, 22, 29, May 3—**Therapeutic Movement, Manipulation and Massage.** UCLA. Tuesdays.

April 9-11—**Bacteriology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 20 hrs. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 9-12—**Nosocomial Infection.** Memorial Hospital Medical Center-UCI Center for Health Education. Wednesday-Saturday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 13-25—**Mental Retardation.** UCLA. Two weeks.

April 17-19—**Wound Management Workshop.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday.

April 21-26—**1980 Family Practice Review.** PMC at Claremont Hotel, Berkeley. Monday-Saturday. 27 hrs. $350.

April 24-27—**Postgraduate Institute.** CMA and USC at Ahwahnee Hotel, Yosemite. Thursday-Sunday. Contact: Charlotte Newhart, CMA.

April 26-27—**Deafness: The Silent Barrier to Health Care.** UCSF. Saturday-Sunday. Contact: UCSF, Cont. Ed. in Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland, OR 97227. (503) 280-3200.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

February 11-15—**Eleventh Annual Family Practice Review.** Portland, Monday-Friday. Hilton Hotel. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OF INTEREST TO ALL PHYSICIANS

February 10—**What's New in Perinatal Medicine—March of Dimes Birth Defects Foundation and The Oregon Academy of Family Physicians.** Portland, Sunday. Jantzen Beach, Red Lion Inn. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 17-20—**American College of Physicians Review Course.** Portland, Tuesday-Friday. Jantzen Beach Thunderbird. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 25-27—**Symposium on Sports Medicine.** Eugene, Wednesday-Friday. Thunderbird Motor Inn. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

December 14-15—**Orthopedics for the Family Physician.** Seattle. Friday-Saturday. Swedish Hospital and Medical Center. Contact: John L. Wright, MD, Swedish Hospital and Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2265.

January 8, 10, 12—**The Geriatric Patient.** Tacoma. Tuesday, Thursday, Saturday. Puget Sound Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 S. 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

January 12—**Conference on Obstetrics and Gynecology.** Seattle. Saturday. Providence Medical Center. Contact: Evelyn Foote, Continuing Education, Providence Medical Center, 500 17th Ave., Seattle, WA 98122. (206) 326-5821.

January 17-18—**Pediatric Update.** Seattle. Thursday-Friday. Children's Orthopedic Hospital and Medical Center. Contact: W. O. Robertson, MD, COHMC: ZC-10, 4800 Sand Point Way NE, Seattle, WA 98105. (206) 634-5072.

January 23-February 1—**Critical Care I and Ski.** Val Gardenia, Italian Alps. Ten Days. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

January 25—**Current Urological Considerations.** Seattle. Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

January 26—**Useful Radiology in Primary Care—Part I: Above the Diaphragm.** Seattle. Saturday. Group Health, Sixth Floor Conference Facility. Contact: Jackie Taylor, Group Health Cooperative of Puget Sound, 201 16th Avenue E, No. 321, A-5, Seattle, WA 98112. (206) 326-7349.

January 26—**Rheumatology.** Tacoma. Saturday. St. Joseph Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

January 29-30—**Tax Estate and Financial Planning.** Seattle. Tuesday-Wednesday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

January 31, February 1-2—**Neuro-ophthalmology—Annual President's Meeting.** Seattle. Thursday-Saturday. Olympic Hotel. Contact: Marcia Wahlman, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Room 900, Seattle, WA 98121. (206) 623-4801.

February 1-2—**Violence in the Family.** Seattle. Friday-Saturday. Swedish Hospital Auditorium. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 5-8—**Ski and Learn.** Crystal Mountain, WA. Thursday-Friday. Contact: Carolyn M. Palmer, Washington Academy of Family Physicians, 3700 140th Ave., NE, Bellevue, WA 98005. (206) 883-8852.

February 8-9—**Workshops in Endocrinology.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

February 9-16—**Sun Valley Critical Care: Maternal/Perinatal.** Sun Valley, Idaho. Saturday thru Saturday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 15—**Peripheral Vascular Disease.** Tacoma. Friday. Tacoma General Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

February 18—**Endocrinology Circuit Course.** Vancouver, WA. Monday (4 hours). St. Joseph Community Hospital. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 19—**Endocrinology Circuit Course.** Longview. Tuesday (4 hours). Monticello Medical Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 20—**Endocrinology Circuit Course.** Olympia. Wednesday (4 hours). Tyee Motor Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 21—**Endocrinology Circuit Course.** Bremerton. Thursday. Harrison Memorial Hospital. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 22—**Endocrinology Circuit Course.** Bellingham. Friday. Western Washington University. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 22-23—**Psychiatric Management of the Problem of Pain.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

February 23-March 1—**Office Orthopedics for Primary Physicians.** Sun Valley, Idaho. Saturday-Saturday. Sun Valley Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 28-29—**Northwest Stroke Symposium.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: Education and Training Department, Northwest Hospital, 1551 North 120th, Seattle, WA 98133. (206) 364-0500, ext. 686.

March 6-7—**American College of Physicians Medical Knowledge Self-Assessment Program V (MKSAP V).** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 8-15—**Psychiatry for Primary Physicians.** Sun Valley, Idaho. Saturday-Saturday. Sun Valley Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 9-15—**Critical Care II and Ski.** Lake Tahoe, Nevada. Thursday-Wednesday. Sahara Tahoe. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

March 13-14—**Tacoma Academy of Internal Medicine Annual Scientific Program.** Tacoma. Thursday-Friday. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

March 14-15—**Pharmacology for the Practitioner.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

March 15-22—**Sports Medicine.** Sun Valley, Idaho. Saturday-Saturday. Sun Valley Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 17-28—**Rehabilitation Medicine Review.** Seattle. Two weeks. University Towers Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 21-22—**Days of Pediatrics.** Tacoma. Friday-Saturday. Mary Bridge Children's Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98450. (206) 627-7137.

March 24-28—**Advances in Family Practice.** Seattle. Monday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 29-April 5—**Infectious Diseases.** Hilo, Hawaii. Saturday-Saturday. Naniloa and Kona Surf Hotels. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 31-April 3—**American College of Physicians: Hematology.** Seattle. Monday-Thursday. Olympic Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 3-4—**Hazards to the Fetus.** Seattle. Thursday-Friday. Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 10-11—**Dermatology.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 10-11—**Annual Cancer Symposium—Gastrointestinal.** Seattle. Thursday-Friday. Swedish Hospital and Medical Center. Contact: John L. Wright, MD, Swedish Hospital and Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2265.

April 12—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

April 17-18—**Couples.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 18-19—**Tacoma Surgical Society Annual Scientific Program.** Tacoma. Friday-Saturday. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

April 24-25—**Respiratory Care.** Seattle. Thursday-Friday. Contract: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 24-25—**Review of Arrythmias.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 25-26—**Anesthesia: Low Flow States—Pathology and Treatment.** Vancouver, British Columbia. Friday-Saturday. Four Seasons Hotel. Contact: Dr. K. Turnbull, Academy of Medicine, 1807 West 10th Avenue, Vancouver, BC V6J 2A9.

May 1-2—**Controversies in Medicine.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 2-3—**Contemporary Clinical Neurology.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 8-10—**Washington Academy of Family Physicians—Annual Scientific Assembly.** Seattle. Thursday-Saturday. Red Lion Inn/Seattle-Tacoma Airport. 14 prescribed hours. Contact: Carolyn M. Palmer, Washington Academy of Family Physicians, 3700 140th Ave., NE, Bellevue, WA 98005. (206) 883-8852.

May 16-17—**Medical Applications of Real-Time Ultrasound.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 22-23—**Adolescent Medicine.** Seattle. Thursday-Friday. Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 30—**Ophthalmology in Family Practice.** Seattle. Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 5-6—**Medicine and the Law.** Port Ludlow. Thursday-Friday. The Admiralty. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 6-7—**Workshops in Musculoskeletal Disease.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 12-13—**Renal Disease.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 12-13—**Regional Anesthesia and Nerve Block.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 19-20—**Laboratory Medicine.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 26-27—**American College of Physicians Medical Knowledge Self-Assessment Program V (MKSAP V).** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 28-July 5—**Alaska Cruise—Emergency Medical Care: Trauma, Orthopedics and Surgery; Biomedical History.** 8 days. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

January 23—**Management of Premature Labor—Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

February 7—**Diagnosis of Organic Brain Syndrome—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

March 20—**Treatment Outcome Study, Harborview Community Health Center—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

March 26—**Utilization of Midlevel Practitioners—Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday. 12 noon,

Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

May 1—**Child and Community Psychiatry—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

May 28—**Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday, 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

June 19—**Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

MONTANA

January 9—**Pediatric Neurology—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

January 23-25—**Health Advice for Travelers; New Developments in Diagnosis and Therapy of Parasitic Disease—Univ. of Wash. Internal Medicine Review Sessions.**

January 23, Wednesday, Great Falls. 4:30-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

January 24, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

January 25, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

February 13—**Pediatric Arthritis-Immunology—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 20-22—**Diagnosis and Management of Bleeding Disorders—Univ. of Wash. Internal Medicine Review Sessions.**

February 20, Wednesday, Great Falls, 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 21, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

February 22, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

February 23-24—**Annual Mid-Winter Meeting, Montana Academy of Dermatology.** Big Sky. Saturday-Sunday. Huntley Lodge. Contact: John R. Tkach, MD, 300 N. Willson, Bozeman, MT 59715. (406) 587-5442.

February 29-March 1—**Annual Medical Seminar.** Big Sky. Friday-Saturday. Huntley Lodge. Contact: D. Frank Johnson, MD, Interhospital Continuing Medical Education Department, Marillac Hall, Billings, MT 59101. (406) 657-7083.

March 12—**Pediatric Hematology—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 26-28—**The Eye and Internal Disease—Univ. of Wash. Internal Medicine Review Sessions.**

March 26, Wednesday, Great Falls. 4:30-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 27, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

March 28, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

April 9—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 16-18—**Office Gynecology—Univ. of Wash. Internal Medicine Review Sessions.**

April 16, Wednesday, Great Falls. 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 17, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

April 18, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

May 7—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 28-30—**Nuclear Medicine for Internists—Univ. of Wash. Internal Medicine Review Sessions.**

May 28, Wednesday, Great Falls. 4:30-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 29, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

May 30, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 52 West Pine, Missoula, MT 59801. (406) 549-3782.

June 11-13—**Transient Ischemic Attack and Stroke; Seizure Disorders—Univ. of Wash. Internal Medicine Review Sessions.**

June 11, Wednesday, Great Falls. 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

June 12, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

June 13, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

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January 22—**Pediatric Surgery—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

January 30-February 3—**Seminar in the Snow: A Postgraduate Course in Emergency Medicine.** Elkhorn Village, Sun Valley. Wednesday-Sunday. Contact D. Craig Dennis, MD, 897 MacArthur Blvd., San Leandro, CA 94577. (415) 632-1504.

February 9-16—**Sun Valley Critical Care: Maternal/Perinatal.** Sun Valley, Idaho. Saturday thru Saturday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 23-March 1—**Office Orthopedics for Primary Physicians.** Sun Valley. Saturday-Saturday. Sun Valley Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: June 6-9, 1980, McKinley Village Lodge.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 23-27, 1980, Registry Resort, Scottsdale.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: February 8-13, 1980, Town and Country, San Diego.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: 1980—date and place to be announced.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: 1980—date and place to be announced.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1980, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 2-4, 1980, Bozeman.

Nevada State Medical Association—3360 Baker Lane, Reno 89502. Annual Meeting: May 16-18, 1980, MGM Grand, Las Vegas.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 7-9, 1980, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Meeting: 1980—date and place to be announced.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: 1980—date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 2-5, 1980, Thunderbird at Jantzen Beach, Vancouver, WA.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 23-27, 1980, Snow King Inn, Jackson.

February 26—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

March 1-8—**Current Concepts in Medicine—Good Samaritan Hospital, San Jose, California.** Sun Valley. Saturday-Saturday. Contact: Daman-Nelson Travel, 115 Mission St., San Francisco, CA 94105. (415) 982-3307.

March 8-15—**Psychiatry for Primary Physicians.** Sun Valley. Saturday-Saturday. Sun Valley Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 15-22—**Sports Medicine.** Sun Valley. Saturday-Saturday. Sun Valley Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 17—**Shock in Pregnancy—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

March 25—**Pediatric Arthritis and Immunology—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

April 14—**Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

April 22—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

May 19—**Hypertension and Pregnancy—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

May 20—**Dysmorphology—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony's Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

Index to
The Western Journal of Medicine Advertising

BANK OF AMERICA
Business Services 23
BURROUGHS WELLCOME CO.
Zyloprim 2
CALIFORNIA MEDICAL ASSOCIATION
109th Annual Session 27
CALIFORNIA MEDICAL EDUCATION AND RESEARCH FOUNDATION 28
CLASSIFIED 20, 22, 24
COLLEGE OF AMERICAN PATHOLOGISTS 10
DOCTORS' COMPANY, THE 21
ELI LILLY AND COMPANY
Keflex 19
FIRSTMARK CAPITAL CORPORATION 14
HOLY CROSS HOSPITAL
New—Sleep Disorders Center 14
HOME FEDERAL SAVINGS 16
HOSPITAL OF THE GOOD SAMARITAN, THE
Testicular Tumors 29
INSURANCE CORPORATION OF AMERICA 8, 9
MEAD JOHNSON PHARMACEUTICAL DIVISION
Duricef 17, 18
MERCK SHARP & DOHME
Aldoril 26
POWERS/DIRTH LIMITED 25
PRESTO FOOD PRODUCTS INC.
Mocha Mix 6
ROCHE LABORATORIES
Gantanol ..... 2nd Cover, 1, 2
Valium ..... 3rd and 4th Covers
SANDOZ PHARMACEUTICALS
Hydergine 7
SMITH KLINE & FRENCH LABORATORIES
Tagamet 15
USC SCHOOL OF MEDICINE
28th Annual Intensive Review 26
UNIVERSITY MICROFILMS INC. 30
UNIVERSITY OF UTAH
Snowbird Conference 26
UPJOHN CO, THE
Mutrin 11, 12, 13 14
UTAH OPHTHALMOLOGICAL SOCIETY
Annual Winter Meeting 26
WOODSIDE CAPITAL CORPORATION 2

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